IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF NEW JERSEY

ELI LILLY AND COMPANY, : Civil No. 07-cv-3770-DMC

Plaintiff, :

v. : TRANSCRIPT OF TRIAL PROCEEDINGS

ACTIVIS ELIZABETH LLC, : VOLUME 1
GLENMARK PHARMACEUTICALS INC., USA,
SUN PHARMACEUTICAL INDUSTRIES LIMITED, :
SANDOZ INC., MYLAN PHARMACEUTICALS INC.,
APOTEX INC., AUROBINDO PHARMA LTD., :
TEVA PHARMACEUTICALS USA, INC.,
SYNTHON LABORATORIES, INC., :
ZYDUS PHARMACEUTICALS, USA, INC.,
:
Defendants.
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Newark, New Jersey
May 18, 2010

BEFORE:

THE HON. DENNIS M. CAVANAUGH, U.S.D.J.

Reported by
CHARLES P. McGUIRE, C.S.R.
Official Court Reporter

Pursuant to Section 753, Title 28, United States Code, the following transcript is certified to be an accurate record as taken stenographically in the above entitled proceedings.

s/CHARLES P. McGUIRE, C.S.R.

CHARLES P. McGUIRE, C.S.R.

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THE COURT CLERK: All rise.

THE COURT: Be seated.

Good morning.

Well, I guess we're starting a trial today.

This is Lilly v. Activis, et al, Civil Action Number 07-3770.

I guess for the record we should start by getting those of you who are willing to put your names on the record.

MR. LIPSEY: Good morning, Your Honor.

Charles Lipsey, Finnegan Henderson, for Plaintiff Eli Lilly and Company.

I'm joined at counsel table today by my partner from Finnegan Henderson Laura Masurovsky, by my partner Mr. Scott Burwell, and from Eli Lilly and Company, Mr. Mark Stewart --

MR. STEWART: Good morning, Your Honor.

MR. LIPSEY: -- and Mr. Tonya Combs. We may have a different cast of characters as the trial progresses.

THE COURT: I understand.

Anyone else here on behalf of Plaintiff who wishes to get on the record?

MR. BRENNER: Your Honor, John Brenner, Pepper Hamilton, also on behalf of the Plaintiff.

MR. BAJEFSKY: Your Honor, Robert Bajefsky,

Finnegan Henderson.

THE COURT: All right. Now let's start on the other side.

MR. CLEMENT: Thank you, Your Honor.

Alan Clement from the firm of Locke Lord Bissell & Liddell on behalf of Defendant Apotex, and with me I have Miki Goodin, Joe Froehlich, David Green, and David Abramowitz from our firm as well.

THE COURT: Okay.

MR. ROCKEY: Good morning, Your Honor.

Keith Rockey and Eric Abraham --

MR. ABRAHAM: Good morning, Your Honor. Eric Abraham from Hill Wallack, also for Defendant Sandoz.

MR. ROCKEY: I'm from the firm of Rockey Depke & Lyons in Chicago. With me is my partner Kathy Lyons, somewhere.

MR. ABRAHAM: We also after from Sandoz Alexandra Haner and Pearl Siew in the courtroom. Thank you.

MS. FLAX: Good morning, Your Honor.

Melissa Flax from the law firm of Carella Byrne on behalf of Aurobindo. With me at counsel table from the law firm of Rakoczy Molino Mazzochi Siwik is William Rakoczy. Also in the courtroom is Christine Siwik as well as Robert Teigen and Gregory Duff.

THE COURT: Okay. Thank you.

MR. PARKER: Good morning, Your Honor.

Tom Parker from the law firm of Alston & Bird, representing Mylan Pharmaceuticals. In the courtroom with me this morning, Your Honor, is our local counsel, Arnie Callmann.

MR. CALLMANN: Hello, Your Honor.

MR. PARKER: And also, Your Honor, I have with me Vicki Spataro from the law firm of Alston Bird also here on behalf of Mylan, and also Mylan's in house counsel, Andrea Triglio.

THE COURT: Thank you.

MR. HURST: Good morning, Your Honor.

Jim Hurst, I'm from Winston & Strawn, and we're here on behalf of Sun Pharmaceutical Industries. I'm here with my partners, James Richter and Gail Standish.

MS. STANDISH: Good morning, Your Honor.

MR. RICHTER: Good morning, Your Honor.

THE COURT: Anyone else that needs to get on the record before we continue?

All right. I hope there's not going to be a test as to who --

(Laughter)

THE COURT: I'll do my best, but most of you will be addressed as "counsel."

All right. Well, basically, we have here a

challenge to the Eli patent, the 5,658,590 patent by Defendants, who claim that the patent is invalid and/or unenforceable based on lack of enablement and utility, obviousness, and inequitable conduct before the Patent Office. The '590 patent is a method of use patent which claims methods of treatment for Attention Deficit/Hyperactivity Disorder, ADHD, with atomoxetine. Claim 1 of the patent covers a method of treating Attention Deficit/Hyperactivity Disorder comprising administering to a patient in need of such treatment an effective amount of tomoxetine. Claims 2 through 16 cover specific treatment plans for subtypes of ADHD and for certain groups of patients.

This Court has had the benefit of -- call it benefit --

(Laughter)

THE COURT: -- of dispositive motions that we've ruled upon, and more recently a significant number of in limine applications, also ruled upon.

I will not revisit any of those applications. Plus, Judge Falk has issued several opinions, one in particular regarding an expert, Dr. Paul, I believe, which I will also adopt.

I believe that it's been decided -- it's been agreed that in this juxtaposed Plaintiff-Defendant situation

under Hatch-Waxman that the Defendants will go forth with their case-in-chief, then the Plaintiffs, and then we'll deal with rebuttal.

Just so those of you who haven't been here before should be aware, I want this to be a pleasant experience. I'm a great believer in civility and promptness. Maybe I should change that: I'm a great believer in promptness --

(Laughter)

THE COURT: -- and civility. We have a lot of people, a lot of claims, a lot of important information that has to get out here. So it would be my plan -- I'm going to tell you how my plan is to move this along and then I'm going to tell you why I have to be away for a couple of days. It's my plan to start every day by at least nine o'clock, I may adjust that to earlier, and to end each day around four. I may adjust that to later, depending.

This week, we will go today and tomorrow, we will probably stop tomorrow around 3:30 or so. It is necessary that I go to -- my son, my last son will be graduating college on Saturday, so we're going out to his college, and so I will not be here on Thursday and Friday. I will be back, of course, hopefully on Monday.

The other scheduling problem that I see is, I guess this will carry, I think counsel have suggested perhaps 12 trial days, 10 to 12, something like that. I

guess that will run us into Memorial Day, so we will lose that Monday, whatever day of the week that is, Rob, 29th or something, whatever it is. And then in the event we do have to go further, there are issues about a couple of you having to appear before the Circuit, I think on the 3rd and 6th of June.

MR. LIPSEY: The 7th, Your Honor. Hopefully we will not be here, but just in case.

THE COURT: I'm hopeful, too.

MR. RAKOCZY: And I have an appearance on June 3rd, Your Honor, before the 3rd Circuit. Thank you.

THE COURT: Okay. Well, of course, since the Circuit has chosen not to make an adjournment, this Court, always being the bastion of reason, will.

(Laughter)

THE COURT: And I will certainly allow counsel to appear before the Circuit if that occurs.

Again, for those of you that haven't been before me before, I do try to move things along. I try not to be too difficult about that, but I find that, especially with good attorneys who are prepared, which I'm sure I have before me, that at the end of the day, the attorneys also appreciate it. I don't like much down time. I recognize we don't have a jury here to deal with, so I will be as flexible and I will try to be as accommodating as I can to

you. I know some of you are from out of state, and you have to make a lot of arrangements. I know what it's like to have to try a case and the difficulties and the time consumption for you when you're not in court. So, again, I will try my best to accommodate you while still trying to move this along at a reasonable rate. I do have another trial right after this that's been around forever and I'm going to have to get to that too, but I don't plan to give anyone here short shrift.

Now, I also know that there was a request for the ability to put on a two-hour tutorial or thereabouts. I have denied that request only because I don't think it's necessary in that I have paid a lot of attention to this case, I've had, as I said at the beginning, the benefit of a lot of motions, which gave me the opportunity to read a whole lot about the case, and I think that the same benefit can occur when that individual, who I think is the main expert on behalf of Plaintiff, when that gentleman has to testify, he can expand his testimony to explain that which he has to explain, within reason.

All right. I think I have taken care of -- what are your plans -- on the last one of these I had where I had a cast of characters, there were issues, just mundane issues of what you're going to do for lunch, where you're going to do it, how you're going to do it. We have tons of people

here. Because I really don't want to be breaking for lunch and then have to wait around for two hours and three hours for people to get back. So to the extent that's an issue logistically, perhaps you can speak -- if you haven't already taken care of this, I know you have local counsel, perhaps they've helped you -- with my deputy, Scott Creegan. I know the last time, we set aside a couple of rooms for some individuals so you could have your lunch brought in and didn't have to be running all over the city. But I'll leave that to you. Maybe some of you don't plan on eating, I don't know.

All right. Well, that said, is there anything that we have to get on the record before we begin?

(No response)

THE COURT: All right. What is the order that we're going to go in as far as the Defendants?

MR. CLEMENT: I believe Defendants are going to start with the opening.

THE COURT: I know that. But which Defendant? What's the order of Defendants?

MR. CLEMENT: I'm going to do part of the opening. I think you've given us 45 minutes for the opening, Your Honor. I'm going to take up about 25 minutes, and then my colleague, Mr. Rokoczy, is going to take up the other 20.

THE COURT: But I mean which client, which

Defendants will be going? In what order?

MR. CLEMENT: We're trying to do it in a joint manner in order to expedite things.

THE COURT: Because I'm not going to have to worry about everybody getting up and all of that.

MR. CLEMENT: No, it's just going to be two of the Defendants' attorneys speaking at the opening, Your Honor.

THE COURT: Okay. Thank you.

All right. Counsel, I'll hear you.

MR. CLEMENT: Thank you, Your Honor.

Your Honor, I have a couple notebooks I'd like to hand up with the slide presentation.

THE COURT: And to the extent anybody has any telephones or any of those other annoying devices, could you just please put them on silent or something so we don't interrupt counsel while they're in the midst of their presentations? Thank you.

MR. CLEMENT: Thank you very much, Your Honor.

My name is Alan Clement. I'm with the firm of Locke Lord Bissell & Liddell, and I represent Defendant Apotex in this case.

Your Honor, we're here on the following issues: Obviousness, nonenablement for lack of utility, secondary considerations, nonenablement to the full claim scope, and inequitable conduct.

I'm going to be addressing the first three, and then, as I said, Mr. Rakoczy will finish the opening addressing the last two.

Invalidity, Your Honor, always starts with looking at the patent claim, and the claim here is a method of treating ADHD comprising administering to a patient in need of treatment an effective amount of tomoxetine. It's a simple claim. We haven't even had any disputes about -- Markman disputes about claim construction.

Claims 2 to 16 are dependent claims either directly or indirectly from claim 1. They really don't add much, just a few details. I don't think any of the parties are asserting any of those details with regard to obviousness. We all pretty much agree they rise or fall together.

Your Honor, we can't talk about obviousness without looking at the Graham factors. I'm sure you're aware of them. I just want to run through them briefly here: Level of skill in the art; scope and content of the art; differences between the art, and the claims as issue, and by following these factors, you avoid problems with hindsight.

We also cannot talks about obviousness without talking about the KSR case. And one thing the KSR case did was affirm that obviousness can be established by an

obviousness to try standard. In the KSR case, it said: "When there is a design need and there is only a finite number of identified, predictable solutions that leads to anticipated success, we have invalidity based on obvious to try."

If you turn back to the Graham factors, Your Honor, the first factor is level of skill in the art. There's really not much dispute about it. It's a very high level here.

Let's turn to the prior art, the scope of the prior art, and the prior art that the Defendants are relying on.

Okay. What art is it the Defendants are relying on? We are relying on Donnelly in view of Bolden-Watson and Fuller & Wong. We rely on Donnelly to teach that desipramine, which is another compound, it was an antidepressant, but it was also used to treat ADHD, it specifically blocks -- it operates by having a known mechanism of selectively blocking norepinephrine reuptake, and desipramine also was known to have less neuronal receptor activity, which caused it to have fewer side effects .

In combination with Donnelly, the Bolden-Watson and Fuller & Wong references show that there was a known compound at the time the '590 patent was filed known as

atomoxetine, and that like desipramine, atomoxetine had the known mechanism to specifically block norepinephrine reuptake, and also like desipramine, it had less neuronal receptor activity and less side effects. And this combination, Your Honor, leads to the conclusion that the '590 patent claims are obvious.

Let's turn to the Donnelly reference and take a look at it briefly.

Your Honor, this is a picture of the Donnelly reference. It's a 1986 publication, and it discussed the study for the efficacy of using desipramine to treat ADHD. And right in the abstract, Your Honor -- and Dr. Berridge is going to testify at length regarding this -- right in the abstract, it says that the authors find desipramine to be effective in treating ADHD. That "DMI" in that top right box, that's shorthand for desipramine.

In the bottom box, the abstract shows that the authors also found why they thought desipramine treated ADHD. And they use these words: "These data corroborate previous findings on sympathomimetic effects..." Your Honor, as Dr. Berridge will explain, that's just a fancy way of saying that the findings support that drugs with a noradrenergic mechanism treat ADHD. Noradrenergic and noradrenaline -- norepinephrine, I'm sorry, are one and the same thing. There's no dispute about that.

Okay. What else does Donnelly say?

It talks a little bit about receptor activity and side effects. On the second page of Donnelly, Dr. Berridge will explain that desipramine has less receptor activity and therefore has a reduced side effect profile than the other TCAs. Other than desipramine, there are other known conducts like imipramine, nortriptyline. They are known as the TCAs.

So what Donnelly is saying, Your Honor, is that desipramine is a better TCA for treating ADHD because it works, and it has the benefit of less side effects. This leaves a person of ordinary skill in the art with the thought that if I can find another drug with similar norepinephrine reuptake inhibition properties and less receptor activity, that also should be reasonably anticipated to work to treat ADHD.

And was there another such drug out there? Yes, there was: Atomoxetine, as taught by Defendant's secondary references, Bolden-Watson and Fuller-Wong.

Let's first take a look at Bolden-Watson, Your Honor. This is DTX-22, and Dr. Berridge is going to speak at length about this, and he's going to explain that Bolden-Watson contains data from which the person of ordinary skill in the art can conclude that atomoxetine, like desipramine, has selective norepinephrine reuptake

inhibition properties.

The next reference Defendants rely on is Fuller & Wong, and whereas Bolden Watson talked about the reuptake selectivity, Defendants rely on Fuller Wong to talk about the receptor activities and the reduced side effects. Dr. Berridge is going to explain that this reference also has data from which one can tell that atomoxetine has reduced receptor activity and a reduced side effect profile.

So that takes us to the last Graham factor, the differences between the prior art and the claims at issue. And going back to my earlier chart, the only thing that the prior art doesn't show is that atomoxetine had been used at the time of the patent to treat ADHD. It was never explicitly described in the prior art.

However, Your Honor, it would have been obvious to try atomoxetine for the treatment of ADHD because, under the KSR obviousness to try analysis, desipramine was effective in treating ADHD and it had the pharmacological mechanism of being a selective norepinephrine reuptake inhibitor, and if another ADHD treatment was desired, there were only a finite number of selective norepinephrine reuptake inhibitors. Atomoxetine was a known selective norepinephrine reuptake inhibitor with low receptor activity, just like desipramine, and a person of ordinary skill in the art would reasonably expect atomoxetine with those similar selective

norepinephrine reuptake inhibition properties and even lower receptor activity to work to treat ADHD.

Your Honor, that is obvious to try, and the prior art therefore compels the conclusion that the '590 patent claims are obvious and invalid.

I want to turn next to our invalidity based on nonenablement utility argument.

Nonenablement utility, as Your Honor knows, comes from the patent statute 35 U.S.C. 112 which requires an inventor to show he had a useful invention at the time of filing. He cannot just file a patent application based on a hypothesis or a research plan.

And what's interesting here, Your Honor, is the interplay between obviousness and nonenablement utility. It's created what I believe is an insoluble dilemma for Lilly. I know in Lilly's trial brief, they assert that utility is not the flip side of obviousness; and while that may be true, where a patent actually provides data showing something's useful, it is not true when the patent's completely devoid of any such data. And that's exactly what we have here, and that was the same as was the case in the Federal Circuit decisions of In Re 318 and Rasmussen, among others.

Lilly's dilemma is this: The law under the 318 case is at the time you file your invention, you need to

establish utility, either by providing data or providing a rationale as to why the invention has utility. It is clear, as Your Honor already found in the summary judgment rulings, that the '590 patent does not have any data to show utility. Thus, Lilly must rely on some sort of rationale to show utility. The only rationale for Lilly to rely on is the teachings of the prior art, and, if the teachings provide that rationale, then the patent is invalid for obviousness. If the teachings don't provide that rationale, then there's no utility to the patent. So therefore, Your Honor, I think you have to either find the patent obvious or invalid for nonenablement, lack of utility.

If we take a look at the next slide, I think this is very important, so I just want to point to, I want to show you this in pictorial form as well.

As I've said, enablement requires either data in the patent or rationale. Here, there's no question there's no data establishing utility in the patent. Therefore, Lilly needs to rely on the prior art. And if the prior art, as Lilly argues, does not demonstrate that it, atomoxetine, is useful for treating ADHD, then we go up the right-hand side and we find it invalid as not enabled.

However, if, as Defendants argue, the prior art does teach that atomoxetine is useful for treating ADHD, then it compels the conclusion that the patent is invalid

for obviousness. It's an insoluble dilemma.

All right. First, let's talk about whether the patent did provide any data to establish utility.

And Your Honor did review this during the summary judgment stage and came to the correct conclusion at page five of your opinion which denied Lilly's request for reconsideration that there was no data in the patent to establish utility. But I do want to walk through the patent, I think it will be instructive, one portion at a time.

The first portion of the patent is the field of the invention. It merely says that the invention belongs to the pharmaceutical chemistry and psychiatric medicine fields. There's no data in there to support utility.

The next section is the background. This mostly talks about the stimulants that were used to treat ADHD and the TCAs, including desipramine, that were used to treat ADHD. Of course, it omits talking about the teachings I discussed, that selective norepinephrine reuptake inhibition was important, but they did mention the TCAs.

So there's nothing in there for Lilly to rely upon to show utility.

The next section is the summary of the invention. It's merely a conclusory statement repeating the claim. No evidence of utility, not any help to Lilly.

The next section, "Detailed Description." The first paragraph of the detailed description just talks about tomoxetine being a well-known drug and that it had selective norepinephrine reuptake inhibition properties, just like we discussed with the prior art. But this is of no help to Lilly in establishing utility. There's no data there, either.

Okay. Let's take a look at the next paragraph on the bottom of column one up to the top of column tow. There they say tomoxetine is a notably safe drug and its use in ADHD is a superior treatment for that disorder. So there, they're trying to say that there is use.

Let's see what the inventor, Dr. Heiligenstein, actually had to say about this paragraph.

(A videotaped deposition of Dr. Heiligenstein was played as follows:

"QUESTION: Let's go back to Exhibit 1, the patent. At the bottom of column 1, line 66, do you see it says "Tomoxetine is a notably safe drug and its use in ADHD in both adults and children is a superior treatment for that disorder because of its improved safety." Do you see that?

"ANSWER: Yes.

"QUESTION: How did you know that on January 11th, 1995?

"ANSWER: I didn't.

"QUESTION: What did -- what did you base that statement on?

"ANSWER: That is a statement that is prepared through the Patent Office, and that is, from my understanding, standard labeling that would be used in the application for a patent."

(Playback stopped)

MR. CLEMENT: In other words, he didn't know where that statement came from, he just made it up. It cannot be used to establish utility.

Let's take a look at the next paragraph. Now, it seems like this one might show some utility. It talks about effective dose ranges that you can use of tomoxetine to treat ADHD. Let's see what Dr. Heiligenstein had to say about this in his deposition.

(A videotaped deposition of Dr. Heiligenstein was played as follows:

"QUESTION: Now, if you turn to column 2, right, line 7?

"ANSWER: Column 2, line 7, yes, okay.

"QUESTION: It talks about the effective dose of tomoxetine for ADHD. And it gives a slew of numbers there. Do you see that?

"ANSWER: Yes, I do.

"QUESTION: Where do those numbers come from?

"ANSWER: It's hypothesis. It's based upon best thinking, so to speak. It was not based upon any information that we had at the time regarding whether or not it could be effective in ADHD, it's hypothesis."

(Playback stopped)

MR. CLEMENT: I think that says it all, Your Honor: "It's hypothesis." This paragraph has nothing about utility. It's just guessing.

Let's turn to the next portion of the patent.

This portion talks about potential dosage, you know, forms that you could put the atomoxetine in. It doesn't say anything about treating ADHD. It doesn't add anything to the utility.

The next portion of the patent also doesn't add anything to the utility. This is just a copy of the diagnostic criteria for ADHD from a book known as the DSM, the Diagnostic Statistical Manual of Mental Disorders. And that just carries over on to the next page. It's a long definition, so it takes up another half of another column of this patent.

Let's continue to look at the next column of the patent or the next portion of the patent.

Here, Dr. -- or the inventors continue to talk about the disease, how it's made up of two components, how it can continue from childhood into adolescence into

adulthood, and then it talks about at the bottom there that tomoxetine is effective in the treatment of ADHD even though the situation of the treated patient may be complicated by comorbidity with one or more additional disorders.

Well, Dr. Heiligenstein has some interesting testimony on that one as well.

(A videotaped deposition of Dr. Heiligenstein was played as follows:

"QUESTION: And then you go on to say, "Tomoxetine is effective in the treatment of ADHD, even though the situation of the treated patient may be complicated by co-morbidity with one or more additional disorders.

"Do you see that?

"ANSWER: I do.

"QUESTION: How did you know that -- what was the basis for that statement in January 1995?

"ANSWER: Well, there is no scientific data that supports that. It's part of a patent application process.

"QUESTION: So you had no scientific data to support that when you filed this application, correct?

"ANSWER: No scientific data from tomoxetine studies.

"QUESTION: Okay. So you didn't know that statement was true or not, it was just part of the application process; is that your testimony?

"ANSWER: My testimony would be that that is part of the filing of an application.

"QUESTION: That this statement just goes in there because you're filing an application; that's your testimony?

"ANSWER: I would have to defer to patent attorney experts as to how these patents are prepared.

"QUESTION: Okay. When you write an article for a peer-reviewed journal that your name is going to go on, do you want to know every statement in there, you know to be true?

"ANSWER: It's very different writing a scientific article from writing a legal document."

(Playback stopped)

MR. CLEMENT: Your Honor, I think that last bit of testimony is particularly compelling. He in fact had no basis for this patent, and he was just making the statements in there without regard to the truth.

The next two paragraphs of the patent, they merely talk about the issues that ADHD causes in people's lives and the needs for treatment of ADHD. Then there's some conclusory statements about the methods. There's no basis here to establish utility, more just boilerplate hoped-for statements.

And the last portion of the patent, of course, is the claims. Those are just conclusory statements, nothing

to establish utility.

Your Honor, as you can see from this brief summary of the patent, you correctly found that there was no data in the patent to establish utility. It was all hypothesis. And the law is that hypothesis cannot support the utility needed for a patent application.

Your Honor's decision was based on longstanding Federal Circuit law that unproved hypotheses or research plans are not proper subject matter for patents, and that's from the In Re 318 case, citing to the Rasmussen case. There is no question, Your Honor, that this invention was not based on anything other than unsupported hypothesis. I showed you a few clips from Dr. Heiligenstein's deposition, but in his deposition, over 30 times, he said his invention was based only on hypothesis.

And it wasn't only Dr. Heiligenstein who said there was no utility at the time of filing the application.

Lilly's own expert, Dr. Pliszka, in deposition said he would have told Heiligenstein his hypothesis was wrong. He says right there at his deposition transcript, page 601: "Right, because at the time I would have said you're wrong. Dr. Heiligenstein's model is not a good model. I think that's what most people were seeing.

So what does Lilly want to rely on for utility?

They want to rely on this Mass. General Hospital

IND study. The problem with that, Your Honor, is that it took place after the filing of the patent, and Your Honor has already considered whether post-filing data can establish utility for the '590 patent, and Your Honor correctly answered that as a no in your decision on Lilly's reconsideration motion. That is the law of the case, and Lilly has no other data.

Lilly having struck out with the results of the MGH IND study now seeks to say there was some utility known before based on an IRB review. An IRB review is an Institutional Review Board that merely reviews proposed studies to make sure that they're ethical, that they're going to be safe. It's based on things like the Nuremberg Code. But in any event, the IRB is insufficient to establish utility because it was never given to the Patent Office. As Your Honor correctly held in your amended opinion regarding the summary judgment motions, information not given to the Patent Office cannot be used to establish utility.

And, Your Honor, even after the MGH IND study was completed, let alone some IRB review, Dr. Heiligenstein himself still did not believe he had made an invention.

In his deposition at page 127, he told us:

"I wasn't even sure after that study -- " -- meaning the MGH IND study -- " -- that in the targeted

population, the primary population to be targeted for treatment, that we could prove the hypothesis."

So I think it's clear the patent, Your Honor, doesn't have information needed to establish utility. Dr. Heiligenstein said over and over and over again that it was a mere hypothesis, that he wasn't sure it would work. Lilly's own expert said it wouldn't work.

This case is just like the In Re 318 case that Your Honor correctly discussed in the summary judgment and reconsideration opinions. And if the '590 patent is not obvious, it is invalid for nonenablement for failure to establish utility.

As the courts have long held, Your Honor, a patent is not a hunting license. It is not a reward for the search, but compensation for its successful completion.

At the time the '590 patent was filed, Lilly and Heiligenstein were still involved in the search. They had not completed the invention.

Okay. Now I want to turn back to -- turn briefly to secondary considerations, Your Honor, sometimes viewed as the fourth Graham factor.

I have a list here of the ones that Lilly is relying on. I don't think that any of these -- none of these have any merit, but I do want to address a few here for your convenience.

On Lilly, we're not sure, they may rely on commercial success and/or long-felt need. We're not sure at this point in time. But Lilly's own documents say the product was not successful and did not satisfy any long-felt need.

I have here up on the screen, Your Honor, DTX-413. It's a page taken from Lilly's global development plan. It's a couple of statements that they pulled from some studies, Strattera benefit studies I guess that they had done.

And I think the middle one is compelling. It says: "What I don't have now is a kid that walks in my door and I say 'That's a Strattera kid.'"

If that's what the doctors are saying, this is not a successful proved satisfying a long-felt need.

And the bottom one: "Some physicians feel embarrassed or that they need to apologize when patients invest time in Strattera with no result."

This is on a Lilly document. If that's what the doctors are saying, this is not a successful product, not satisfying any long-felt need.

Your Honor, you're also going to see some call notes. These provide further evidence that the product was not a success. A call note is when a representative goes to visit a physician, it's what he writes down about his, you

know, sales call after the visit. And we looked at thousands of these, Your Honor, and our experts, Mr. Boghigian and Dr. Staller, are going to testify about these. And on the slide here is a sample of three, but there were many, many more.

The first one: "Strattera is a disaster." This doctor is overall disgusted with the company and the reps. The second one said that Strattera wasn't word a damn, and the third one, well, that doctor left it to expletives to describe what he thought of Strattera.

Finally, Your Honor, I'm going to talk about no unexpected results.

Lilly is relying on a whole litany of unexpected results, mostly things like, the kids can't fall asleep at night, they lose their appetites when they take stimulants. Stimulants needed to be dosed twice a day back then.

The problem with that is that's a legally wrong standard to apply. When you look at unexpected results, you compare it to the closest prior art, not the prior art of Lilly's choosing. The closest prior art, Your Honor, is the desipramine prior art. That's what Defendants are relying on. And those alleged unexpected results are not improvements over desipramine. Desipramine didn't cause the kids to stay up at night. Desipramine did not cause the kids to lose their appetite. Desipramine could be dosed

once a day. And any advantages, Your Honor, that atomoxetine does have over desipramine based on some lower side effects, that was all known at the time of the invention. It's not unexpected. Lilly had tested this drug in depression and urinary incontinence. The properties, the side effect profile of Lilly's drug was known at the time of filing.

I'm now going to pass my time over to Mr. Rakoczy. Thank you, Your Honor.

MR. RAKOCZY: Thank you, Your Honor.

William Rakoczy on behalf of Defendant Aurobindo Pharma Limited.

I will speak briefly this morning to the two remaining issues for trial, the first one being lack of enablement to the full scope of the claims, the second one being unenforceability for inequitable conduct.

The first, really quickly back to enablement, Your Honor.

Just as the patent must establish a credible utility as of the filing date, it must also teach the person of ordinary skill how to make and use that invention to the full scope of the claims without undue experimentation.

And as you've just heard, that is really part of the critical quid pro quo of the patent bargain, Your Honor. In exchange for roping off the field as Lilly has done here,

they have to provide an enabling disclosure, and it has to be sufficient enough such that when the skilled person reads it, they know immediately that the invention would work, and they have to know how to make and use it to get it to work without undue experimentation.

Now, what experimentation is undue? For that, the courts look to a variety of Wands factors. I'll take the Court through just a few of them here, Your Honor, but suffice it to say that the evidence here is going to show that all weight is decidedly against Lilly and in favor of a finding of undue experimentation.

The first two Wands factors are very straightforward and simple, nature of the invention and breadth of claims. Here, the invention, again, is straightforward, the use of atomoxetine for treating ADHD. But it's the breadth of claims here that is even more critical because they cover any conceivable dosage form and any conceivable form of atomoxetine at the time of filing.

This is just a representative list, Your Honor, from Lilly itself of the possible dosage forms that fall within the scope of these claims. Again, this is not exhaustive, this is just some of them. There are these and many more known in 1995, including those like depot injections at the bottom that are pointed out specifically in the specification.

And then we get to the forms of atomoxetine. There's even more forms of the drug itself, because we're not just talking about tomoxetine on its own; we're talking about any form of atomoxetine, including all of its pharmaceutically acceptable salts. Again, this is a list, a representative list, not exhaustive, from Lilly, and it comes out of Lilly's own compound patent for the '081 patent that shows all these different forms of atomoxetine. So we have extraordinarily broad claims here.

Now, Lilly is going to stand up here and tell Your Honor you don't need to worry about any of this. You can just focus solely on the preferred tablet and capsule form.

But that's besides the point, Your Honor. A patent is not enabled just because it enables some so-called preferred form. It has to enable every single mode of practicing the invention, particularly when the specification calls out some very specific dosage forms. You have to enable all of them. You can't just say, I did one, don't worry about the rest, because, again, remember, when the person of skill reads this, he has to be able to figure out how to make it work in all of its forms, and that specification here simply doesn't do that, which leads to -- let me back up a second, Your Honor.

It also bears repeating that the risk of these

broad claims falls on Lilly, not the Defendants. The Federal Circuit has repeatedly warned patentees, be careful of what you ask for when you get broad claims because, when you get them, you have to be prepared to meet the challenge that they're enabled to the full scope.

And again, here, that's a challenge we think Lilly cannot meet given how flimsy this disclosure is.

Which is the next Wands factor, which is the guidance or direction in the specification as well as the presence or absence of example. And this is easy, Your Honor. We could read this specification aloud together in less than a couple of minutes, but there's no point in it because you can look at the summary of the invention, the background of the invention, the field of the invention and none of them say anything about dosage forms, let alone how to make and use them. Even if we go to the details section, misnamed as it is, all we get is a laundry list of dosage forms, tablets, capsules and the like, injectable solutions, depot injections, suppositories and the like. It just names them. It doesn't given anyone a clue how to make or use them.

Now, Lilly is not going to get up here and defend the content of the specification. They can't, because it admittedly does not teach how to make all these things.

What Lilly is going to do instead is they're going

to say, Don't worry about the specification, toss it aside, because the knowledge of one of ordinary skill in the art in 1995 would allow that person to use routine testing to make all of these covered dosage forms.

But there's a problem with that, Your Honor, and that's kind of the rub here and the sleight of hand the Court has to be wary of, because the Federal Circuit doesn't allow you to toss out the specification and rely solely on the knowledge of one of ordinary skill to enable a patent. You can't do that. You have to have an enabling disclosure per se to be sure the knowledge of one of ordinary skill can fill in very minor gaps, but repeat, very minor. You can't just toss the specification and say a person of ordinary skill has enough knowledge, they don't need an enabling disclosure. You can't do that, and the Federal Circuit has repeatedly held that, including a recent case that is on all fours with this one, Alza v. Andrx, which I'll get to in a moment.

Now, the final couple Wands factors, the presence or example -- or presence or absence of working examples, again, that's an easy one. There's nothing here at all, no examples of any kind.

And then the last factor I think is very telling. It's the quantity of experimentation. And here, Your Honor, you're going to hear from the Defendant's expert, Dr. James

Johnson, an expert in formulation with over 40 years of experience in this field. And as you can see just from this slide, which Dr. Johnson will explain in more detail, this is just the preformulation steps necessary to make a depot injection. And all these steps are doing is getting you to the proper form of atomoxetine for the active ingredient. It involves a very complex iterative trial and error process of multiple stages of making the drug and testing the drug, and again, this is just to get to the active ingredient to use. We're not even formulating a dosage form yet. This process alone can take years and millions of dollars.

Then we get to the actual formulation stage, which, again, this is just a representative example of a depot injection, not all the other possible examples. And again, here, once we get the active ingredient, as Dr. Johnson will explain, we now have to go through the formulation steps. Multiple formulations have to be made. They have to be tested in vitro and in vivo. Again, for a depot injection alone, this is a process that can take at least two to five years and many millions of dollars. This is no routine process, as Lilly says; it is a very complex, iterative trial and error process. And in fact, these depot injections are so complex that only a handful of these things have ever been developed in the U.S. So undue experimentation in the extreme.

And, in fact, the type of iterative trial and error process that's involved here is exactly the kind of process that the Federal Circuit recently held amounted to undue experimentation in an almost identical case. That's the Alza v. Andrx case, which involved one of the world's top-selling ADHD medications, Concerta. Now, Concerta contains the stimulant medication methylphenidate. The patent there was also a broad method of use patent which was directed to a method of treating ADHD with a methylphenidate that provides an ascending release rate. The Court broadly construed the claims to cover any methylphenidate dosage form that provides that rate. The problem was, the specification only identified a very particular release mechanism called an osmotic dosage form. Otherwise, it just gave a laundry list like the specification here of other non-osmotic dosage forms but didn't say anything about how to make or use them.

Now, much like Lilly here, the brand company there argued that you don't need to worry about the spec; you can rely on the knowledge of one of ordinary skill in the art even with our minimal guidance in our specification. Again, the Federal Circuit rejected that because you can't solely rely on the knowledge of one of ordinary skill. You have to rely on the enabling disclosure. And even if you could, the iterative trial and error process involved in that case

amounted to undue experimentation. That's exactly what we've got here. We've gotten even broader claims in this case, no guidance or direction in the spec, no working examples, very complex trial and error iterative process to get to these formulations and certainly to get to all of the conceivable dosage forms, and on top of that, again, we get no guidance whatsoever. And as a matter of law, the Court can't just go back to the knowledge of one of ordinary skill.

In the end, this specification is so flimsy, all it's doing is an invitation to the person of ordinary skill, saying, Hey, I've got an idea to use this for atomoxetine, now why don't you go out and try to find out how to use it?

That's the epitome of a nonenabling disclosure.

Now, the last issue, Your Honor, inequitable conduct or unenforceability of the claims.

Your Honor has already identified the withheld prior art references in the summary judgment opinion. Just briefly, they are now known in the record as the Board opinion, which is an opinion of the Patent Board of Appeals and Interferences rejecting -- or affirming the rejection of analogous claims for the same rationale used to reject the '590 patent claims here, and secondly, the so-called tandamine reference, which was from a European search report issued during the prosecution of the foreign counterpart to

the '590 patent. That search report identified the tandamine reference as a particularly relevant or what is known as a wide reference.

Now, I think it's important to put these in context, Your Honor, and discuss very briefly what is not in dispute here.

first off, there's no dispute that Lilly's patent attorneys, Joseph Jones and Robert Titus, neither of which I believe will show up for trial here, were aware of these references. They were intimately involved with the prosecution of this patent. They did not disclose these references to the Patent Office, and I believe they both acknowledged their duty of candor and utmost good faith as well as a knowledge of the MPE regulations governing patent examinations.

Now, materiality and intent. Quickly, on the Board reference, it would be an understatement to say that this would be important to a reasonable examiner. As Mr. Goolkasian will testify, who spent over 10 years on the Patent Board himself, what's important about the Board opinion is not necessarily that it are involves a patent on a method of using atomoxetine for urinary incontinence, but the rationale used to reject that patent, which is the same rationale used in the '590 patent, namely, that tomoxetine was a known inhibitor of norepinephrine reuptake, and that

such reuptake was known in the prior art with compounds like the TCAs to be effective in treating urinary incontinence. The same rationale was used by the '590 patent examiner here. Tomoxetine is known as a norepinephrine reuptake inhibitor, and such reuptake in the TCAs was known to be effective in treating ADHD. Had the Patent Examiner for the '590 patent actually had this Board opinion, he likely never would have let these claims issue because he would have seen that his rationale had been upheld by a binding Bored opinion.

And from the circumstances of these nondisclosures, intent to deceive can easily be inferred. Attorney Jones was not only aware of the Board opinion. He handled it. He actually briefed it. And then he went about doing everything in his power to try and wipe it off the books. He actually went and tried to withdraw it, which is an extremely rare occurrence. People rarely even ask for this kind of relief. They never get it. But he wanted it gone. Why did he want it gone? Because he knew it could be harmful to other cases on atomoxetine.

In addition, Lilly's likely going to tell you that reference is not relevant, or that Jones didn't think it was relevant because it dealt with urinary incontinence.

Also not true, Your Honor. Jones was already submitting references on urinary incontinence.

So the only reasonable inference so be drawn here is that while Attorney Jones was perfectly willing to show the Patent Office other references on urinary incontinence, he was doing everything in his power to hide that Board opinion.

Now, just quickly, Your Honor, the tandamine reference. Again, admittedly material. In addition to refuting an argument in favor of patentability by Lilly, namely, that the TCAs were somehow nonselective or dirty drugs, the tandamine reference directly refutes that. Everybody else in the world, including Titus, thought that this reference was material. The European Patent Office issued this search report saying that it's particularly relevant. This reference was actually used in part to reject claims of the foreign counterpart to the '590 patent, and Attorney Titus himself thought it was relevant because he gave it to the Canadian Patent Office. He has no excuse for not giving it to the U.S. office. A good patent attorney, mindful of his duty of disclosure, always, always submits these particularly relevant search reports to the U. S. Patent Office. In fact, that's why Titus had a regular custom and practice of giving these things to the Patent Office. But he didn't do it here. The only inference to be drawn is he knew it was relevant since he gave it to the Canadian Patent Office. He had a custom and

practice of giving it to the U. S. Patent Office but mysteriously decided not to give this one over. The only inference is, again, that he was hiding this reference from the Patent Office.

So we think that the Court will see evidence from which materiality can be proven by clear and convincing evidence and from which a strong inference of intent to deceive can be inferred.

In sum, Your Honor, the Defendants respectfully request that the Court hold the '590 patent invalid and unenforceable.

Thank you, Judge.

THE COURT: Thank you.

Mr. Lipsey?

MR. LIPSEY: Thank you, Your Honor.

Charles Lipsey, Finnegan Henderson, for the Plaintiffs Eli Lilly and Company.

And as is the custom, I have copies of my slide presentation, which, with the Court's permission, I will hand up, and with the Court's permission I will give to the Court Reporter since it may facilitate transcription.

THE COURT: He needs all the help he can get.

(Laughter)

MR. LIPSEY: We're here about Strattera. The name is atomoxetine. It was called at the time tomoxetine, and

for consistency with the documents, I will refer to it as tomoxetine.

It was the first FDA-approved nonstimulant ADHD drug. And as much as the Defendants wish to denigrate that fact, that was a big deal, Your Honor.

And we're here now to determine whether or not the patent on it is invalid. And the time is gone for accusation and innuendo, and the time is here for the presentation of clear and convincing evidence. It is their burden to prove their allegations by clear and convincing evidence, and we believe they will be unable to do so.

Now, here are some of the advantages and benefits of Strattera. They're right off the label.

It's approved for use in children.

Now, why is that important?

It's important, Your Honor, because desipramine, the stated principal prior art, was not recommended for use in children because of potential dangerous cardiac side effects that I'll discuss in a minute.

It's also approved for adults. It was the first ever medication in the United States approved for the treatment of adult ADHD.

Those next three items, lack of abuse potential, not a Schedule II controlled substance, and once a day dosing are huge practical benefits of parents of children

with ADHD children, and those are actual practical benefits for those.

The last one, approved for maintenance and extended treatment, also has significance because the evidence will show that the prior art tricyclic antidepressants were described as losing effectiveness over time.

Now, there are 10 Defendant corporations on the caption of this case, all of whom are lined up to copy this drug. And while you will hear them tell you what a terrible drug it is, that objective fact speaks volumes about its merit. The fact that they sifted through one million call notes in order to find the three that they showed you proves nothing.

The fact of the matter is, the FDA has found the drug to be safe and effective for these uses, and that is the end of it.

Now, let's talk about obviousness. And I would like to highlight the fact that the obviousness analysis is one in which hindsight is forbidden. It is the great enemy of a proper analysis. And even under KSR, it is the enemy of a proper analysis. And hindsight is exactly what the Defendants have done, because when they showed you the scope and content of the prior art, they didn't show you the whole scope and content of the prior art. They showed you the

selected bits and pieces of it that they thought fit together with hindsight to suggest the invention. And the fact of the matter is, when you see the totality of the prior art, as I will preview for the Court, the conclusion of exactly the opposite is drawn.

So where do we start?

We start with the question of how is it obvious to decide what's going to be a good medication for a disease when you don't know what the cause of the disease is? And the cause of ADHD was unknown and complex.

This McCracken reference; this is from a group at the National Institutes of Mental Health. It was in the center of the development of treatments for ADHD in the 1980's and early 1990's, and even in 1991, and it's true today, as yet, there is no consensus on the precise mechanism of action of ADHD's most commonly prescribed treatment, or of the etiology of ADHD itself.

And why not?

Here is from Donnelly, their principal reference, Your Honor: "The literature describing the neurochemistry of learning and memory is voluminous, complex, and often contradictory," and Your Honor will see that. "Noradrenergic, dopaminergic, cholinergic, serotonergic, peptide, and neurohormonal systems - both central and peripheral - have been implicated in various cognitive

processes."

And that's part of the prior art, Your Honor.

Now, what was in the prior art?

There were a whole variety of ADHD drugs in the art, I have them illustrated here, and they worked in a whole bunch of different ways. There were stimulants. There were inhibitors of the enzyme that breaks down these monoamine transmitters. There were mixed dopamine and norepinephrine reuptake inhibitors, there were the tricyclic antidepressants, which I'll talk about in minute, which had a very broad and diverse pharmacology, and there were these molecules, so-called alpha-2 receptor agonists that bound specifically to receptors, and we will see, as you've been told, tomoxetine doesn't bind to receptors.

So what else do we know?

Their whole thesis is, Oh, it was norepinephrine. A norepinephrine uptake inhibitor is all you need to treat ADHD.

And the problem, Your Honor, is, people who thought very deeply and very long on this had rejected that hypothesis.

Here is Donnelly, their reference: "It is most probable that both noradrenergic -- " -- meaning norepinephrine -- " -- and dopaminergic mechanisms are involved in the mediation of stimulant-induced behavioral

improvement in ADDH."

Here is Zametkin & Rapoport, again from that central group at NIMH. What did they conclude? "It is clear by now that the array of effective agents has put to rest any single transmitter hypothesis."

And what else did they conclude in summary: "Alteration of noradrenergic function appears necessary but not sufficient -- " -- Your Honor, not sufficient -- " -- for clinical efficacy."

You didn't see that slide when they put theirs up.

Moreover, the role of norepinephrine was unclear.

Here again, this is the Shenker reference. It's cited 12 times in the two reports of their expert. It is a detailed review of the literature at the time of 1992, and it points out that even then, the relative roles that dopamine and norepinephrine play in the therapy of ADHD are still unresolved, and they are unresolved today, Your Honor.

And why?

There were confusing signals in the prior art. There was a compound called mianserin. Mianserin was thought to enhance the release of norepinephrine from nerve terminals and create more norepinephrine in the synapse, just the way uptake inhibition does. And what happened? They tested it for ADHD and it didn't work. That's the conclusion that Langer reached.

And then we have opposite conclusion in the prior art. There was a molecule called clonidine that was reported at that time to decrease norepinephrine. But what happened when they tested it? It turned out to be apparently effective in ADHD.

So the point is that norepinephrine was not the answer. The single neurotransmitter hypothesis had been rejected.

How about desipramine?

Desipramine was quite a complicated molecule, as were all of the TCAs, and its mechanism of action was uncertain.

Here is Dr. Biederman from the MGH publishing in 1999 an absolutely unambiguous statement, which, again, you were not shown in their opening: "The pharmacological mechanism of action of DMI -- " -- that's desipramine -- " -- in ADDH remains unknown."

Here's their Donnelly reference. Why was it unknown? It didn't just interact with norepinephrine. It had been shown to affect other neurotransmitters centrally. From their own reference, Donnelly.

And why? This is Ross Baldessarini, the pre-eminent expert at the time on antidepressants, discussing the tricyclic antidepressants, of which desipramine was a prototypical example: "In addition to

blocking the uptake of norepinephrine -- " -- which is all they're talking about -- " -- the tricyclic-type antidepressants exert complex effects on the metabolism, receptors, and functions of monoamines in the brain. It is unfortunate that the drugs used to treat patients at increased risk of suicide are so toxic and potentially lethal."

And that was a major problem with the tricyclic antidepressants.

And it was reflected in the FDA approvals of the day. Desipramine, the holy grail that is now being held up here as the answer to everything, in fact was not recommended for use in children. There was specific reference to the cardiovascular risks, and, in fact, there had been instances of sudden death with the use of desipramine which greatly contraindicated its use.

Now, we will come back to that in a minute. But before we go, it is alleged that because you can see in the literature references to desipramine as a selective norepinephrine uptake inhibitor, well, of course that meant that tomoxetine should be used for the same purpose.

But that's not what the prior art taught, Your Honor. What the prior art taught was that desipramine was relatively selective compared to the other TCAs. And that, again, is from the Biederman 1989 reference. There was a

similar statement in the Donnelly reference that they showed you. Only relatively specific.

And how do we know that?

Well, there's data from Dr. Cusack in 1994 where he measured the affinity of these various drugs for these receptors, and you can see desipramine is in red, imipramine is in blue, and that relative to imipramine, it is relatively selective. It does not have as much activity at these receptors as the other TCAs, but it still has significant utility.

And that was the recognition of people working in the field who knew.

This is Dr. Spencer. Drs. Biederman and Spencer were the ones at MGH who actually tested atomoxetine:

"QUESTION: And desipramine is also a selective norepinephrine reuptake inhibitors?

"ANSWER: No, it's not selective. It has some noradrenergic action, and then some action on lots of other systems, so it's distinctly not selective."

And that, after all, is the point Baldessarini had made: They do lots of things.

Dr. Biederman, to the same effect:

"ANSWER: ...it's a dirtier drug," has other effects on other neurotransmitters.

As to norepinephrine: "It's more than other

tricyclics, but not selective."

Moreover, desipramine's broad actions were implicated in its activities. Again, from people who were in a position to know, Dr. Biederman was asked about TCAs, and he says:

"The TCAs have been found empirically in studies to work in children with ADHD.

"Why?

"Well, we don't know why. I think sometimes we know that things work, and it takes a long time to understand the why. The try six clicks tend to have a very broad effects of various neurotransmitters, norepinephrine, serotonin, histamine, et cetera, et cetera."

And this point is picked up in spades, Your Honor, in the Shenker review. Again, in 1992: "Any discussion of the efficacy of imipramine and desipramine in ADHD must include the fact that, unlike amphetamine, they are fairly potent antagonists of the alpha-1 adrenergic receptor and certain other brain receptors. Whether these properties contribute to or detract from the clinical efficacy remains to be seen."

And that experiment, Your Honor, had not been done as of the filing date of this patent.

Now, into that milieu comes tomoxetine.

Tomoxetine, in contrast, is a truly selective

norepinephrine reuptake inhibitor, and it was pitched as such and touted as such the day it came into the literature.

This is the Wong 1982 publication talking about an inhibitor of "Norepinephrine Uptake Devoid of Affinity For Receptors in the Rat Brain." And that was the major distinction from the day that the properties of this molecule were laid out for people of ordinary skill in the art.

And again, Cusack tells us why. We have here the graph that I showed you comparing imipramine and desipramine, and it also has the data for tomoxetine on there.

And I know what you're thinking: It's missing.

It's not missing, Your Honor. You just can barely see it or not see it at all because it is so much different from desipramine.

Now, even if you double the scale and look at desipramine only, you can barely see the effects of atomoxetine. And that is why tomoxetine is not son of desipramine or desipramine two or desipramine redux; as you've heard, it was a fundamentally different kind of drug.

And, Your Honor, the thing that their evidence will simply be unable to explain and the clearest, most objective indication of why this invention is not obvious is the 13-year delay between the time desipramine -- excuse me,

atomoxetine's properties as a truly selective norepinephrine reuptake inhibitor were described in the literature and the time its benefits in ADHD were recognized. If it were, in fact, so obvious to use it, it would have been mentioned, and it was not.

And then the question is, why not?

Well, the prior art answers that question, too, Your Honor. The prior art taught away from truly selective norepinephrine reuptake inhibitors. Specifically, it focused on other types of drugs.

Now, what they've done in their opening, they've tried to freeze time back in 1984, or 1986. But the fact of the matter is, time moved on and the art moved on, and the art moved on without selective norepinephrine reuptake inhibitors, and that's clear from the literature.

Here again, Zametkin and Rapoport, future directions. What are they suggesting? A combination of dopaminergic and noradrenergic agents.

That's not tomoxetine.

Mefford and Potter from that same group at the NIMH: "The ideal therapeutic agent for treatment of hyperactivity would show a high degree of specificity for uptake into noradrenergic terminals and storage vesicles and possess potent MAO type A activity," and that's not tomoxetine.

McCracken from the same group in 1991. This model would predict that B-HT 920, a selective dopamine autoreceptor agonist drug that also possesses alpha-2 adrenergic agonist properties would be equivalent to stimulants. And that's not tomoxetine either, Your Honor.

Shenker in 1992, reviewing the field. Under the heading of New Drugs: "It may very well be that increased synaptic availability of both dopamine and norepinephrine is required," and that's not tomoxetine, Your Honor.

Under the heading of New Drugs, he talks about a drug called Nomifensine. People had high hope for it because it blocked both dopamine and norepinephrine. It was found to be toxic, as many of these drugs are.

And what does he say? He says new drugs that are both potent blockers of both dopamine and norepinephrine uptake systems have been described elsewhere. And that is not tomoxetine.

Other publications. For example, the Steere publication in 1984 taught the benefit of these molecules that are selective alpha-2A agonists, in other words, a molecule that is intended to bind specifically to the receptor, and that was exactly what tomoxetine did not do.

Back to Shenker. Shenker reviews the field. He has a table. He has a table listing selective drugs that may be useful in behavioral research on ADHD. And what does

he list? He lists 25 different drugs, Your Honor. Not one of them is tomoxetine. He lists half a dozen different categories of drugs. Not one of them is a norepinephrine reuptake inhibitor, a selective norepinephrine reuptake inhibitor.

The prior art had moved on, Your Honor, and had moved on to other things, and people simply had not focused and were not focusing and were not attempting to develop selective norepinephrine reuptake inhibitors, including and specifically those that didn't have the broad spectrum of other receptor activities that the tricyclics had.

There was more. There were the safety concerns that I mentioned. There were the sudden death incidences with desipramine.

And what was said about them? Here's Dr. Riddle in 1993: "It is possible desipramine differs from other tricyclics in ways that make it potentially more lethal." And he explains why.

What's the difference?

"Desipramine's most distinctive feature among the class of tricyclic drugs is that it is the most specific inhibitor of reuptake of norepinephrine."

And if it is possible that that was the sudden-death problem with desipramine, that was a problem that tomoxetine would have in spades, and an excellent

reason why nobody considered using it at the time.

So we come back again to the dilemma in the Defendant's case, which is, if it was so obvious that this molecule was a suitable and superior replacement in ADHD, why did nobody mention it for 13 years?

And the answers are now clear. The prior art taught away. They were looking for other things.

Tomoxetine was known not to have the rich pharmacology that the TCAs had, and therefore, there could have been questions about whether it would be efficacious.

And finally, the desipramine molecule had safety concerns which would have applied in spades to tomoxetine.

All three good reasons why nobody thought of it, and nobody did.

Now, the utility analysis.

We have a profound disconnect on the applicable law. The Court is aware, I think, of our position on it.

There is new news, which we tried to point out, which is that the Federal Circuit in a subsequent en banc decision, the Area (ph) case made it very clear that you cannot require a description in the patent application of what they call an actual reduction to practice, that is an actual demonstration in the laboratory that the invention works. And the argument which you've heard from the Defendants is that we had to have exactly such a

demonstration. That is a gloss on In Re 318 and I would hope at some point to have an opportunity to chat with the Court, hopefully in closing, about what the correct result ought to be.

But even applying the standards that the Court has currently applied, there's a profound difference between the obvious analysis and the utility analysis, whereas obviousness prohibited hindsight, utility requirement mandates it. How? The utility requirement addresses what would be perceived by a person of ordinary skill in the art who was not thinking of this invention to begin with, who had moved on to other things as we have said, who was thinking of going other directions, who, once the invention was made known to them, could they, mining the available prior art with hindsight, reasonably conclude that this was a credible utility. And we think that there is some very substantial evidence in the record to support that that is the case.

First of all, we're not talking about the same disclosure. This is not In Re 318. There were other drugs that credibly and successfully treated this condition. It was not an inherently credible utility. They are described. Their mechanisms are described.

The properties of tomoxetine upon which the asserted utility are based are described in detail, and

specifically, Your Honor, it's said to be notably safe. Notably safe, that was not a guess. Lilly had tested this compound in about a thousand human patients and had a large volume of safety data upon which that statement was made, and that was a sharp distinction from the tricyclic antidepressants.

And then there is the statement, of course, that it can be used in ADHD and that that safety will be an improvement.

The patent also fully describes the state of the prior art.

What else was there?

You've heard this before. There was an operative recipe in there. There was no guesswork about it. It said, here's how you diagnosis the patient. Here is the drug you use. Here is how you use it and how much you use, and, Your Honor, that works. There's no dispute about it. We have the anomalous situation, we're standing here in court with 10 Defendants spending million and millions of dollars because they want to copy a drug that they now claim doesn't work. And of course it works. And the recipe in the patent is an absolutely complete conception of the invention. It is a complete and operative idea of how the invention is to be practiced. And that's all the law requires, Your Honor.

And as Dr. Heiligenstein said, what was it based

on? It was based on best thinking. And there's nothing in the patent law that prohibits making an invention based on best thinking. And this one was fully, completely, and adequately disclosed.

And it works. We will be making an offer of proof that, in fact, that is the very method that's been approved by the FDA, treating patients with ADHD with up to 100 milligrams a day of Strattera, exactly as disclosed.

Now, we think that there is a fundamental distinction here between this case and all the others in the decided cases, and that is, this invention was the subject of an FDA-approved clinical trial under an approved Investigative New Drug Application before the patent application was ever filed. We think there are consequences that flow from that. Let's talk about them for a minute.

Here's Dr. Biederman's testimony:

"QUESTION: And what did you and Dr. Spencer think about Dr. Heiligenstein's ideas?

"ANSWER: Well, we thought it was a good idea that required testing.

"QUESTION: Why did you think it was a good idea?

"ANSWER: Because theoretically the mechanism of action could work in ADHD, but a study is required to see from theory to practice.

"QUESTION: So until the study is completed, you

weren't sure whether in fact tomoxetine would be an effective treatment for ADHD?

"ANSWER: We had no idea."

And that, Your Honor, that is the truth. And if the fact that clinicians need to test in human beings to determine that fully conceived inventions in fact work the way they do, if that's required before you file a patent application and it has to be described in your patent, then I guess we lose. But the one thing you would have to say in that circumstance is there's no way that invention was obvious in that circumstance.

But I suggest to you, Your Honor, even under existing law, it does not require a conclusion that there was no utility.

We will offer into evidence or make an offer of proof, as the case may be, of the certified transcript of the FDA's records of the MGH IND. It contains an indication of a communication on January 3, 1995, before the filing date of this application, that the FDA had approved that application and that MGH was entitled to proceed. It includes by way of a progress report the publication of the results. The publication states the obvious, Your Honor. It states that "The study was approved by our Institutional Review Board, and all subjects provided written informed consent." And those two steps are the result of well

defined regulatory practices in this industry. We will be offering testimony or asking the Court to take judicial notice of that structure. The FDA requires an IRB, an Institutional Review Board, they require approval of the study. "In order to approve research covered by these regulations, the IRB been shall determine that all of the following requirements are satisfied: That "the risks to subjects are reasonable in relation to anticipated benefits," Your Honor. If there are no anticipated benefits, the study cannot go forward.

What does it say about informed consent? Again, the FDA regulations": "In seeking informed consent, the following information shall be provided to each subject: A description of any benefits to the subject or to others which may reasonably be expected from the research." And we have and will offer into evidence the consent form from Massachusetts General Hospital. And what does it say? It says "The benefits of the study are as follows: You may experience improvement in your symptoms if you are assigned to receive tomoxetine."

That was a benefit that gentlemen and women of good will and good skill determined reasonably may be expected from the method. And that was before the patent application was filed.

And that is why, Your Honor, that now puts a

little flesh on the bones of what you heard about already, which is the standard Patent Office practice that when a drug is in clinical trials, the utility is accepted as established, based -- and you can now see that that analysis is based exactly on the regulatory structure which requires these judgments to be made before the significant step of actually putting the drug into a human patient is taken.

"Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, [Patent Office] personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having asserted therapeutic utility."

Now, Your Honor, we contend that any rational construction of the United States Patent Office has to have room in it for this kind of invention, which is sufficiently likely to succeed, that men and women of good skill and good will have determined that ethically you may proceed to testing, and when it in fact works precisely as indicated.

Now, we will also be offering in evidence or making an offer of proof that the results of that study were, in fact, available before the patent issued. They were sent to Dr. Heiligenstein on May 18th. They were published later on in an abstract, again before the patent was issued, and candidly, Your Honor, had the Patent Office

raised any issue about whether that asserted utility was credible, that evidence was available and could have been presented just as it's been for the 60 years before the In Re 318 decision and routinely accepted by the Patent Office. It would be an irrational construction of the patent law to suggest that we should be in a worse position because the Patent Office agreed with us that it was credible than we would have been had they challenged it and we'd come forward with the available evidence.

Now, those are sharp factual distinctions between all of the cases that have been cited here, and much of what's been done here is to read quotable quotes in cases and attempting to apply it to fact patterns that were not there. And I think the Court of Appeals and any experienced trial judge knows you can sometimes get in trouble doing that. We would ask the Court at some appropriate point to take a reasoned view of the technological status of this invention and its being actually in clinical trials and to construe the language in those cases appropriately.

The inequitable conduct analysis.

Our position here is basically that the arguments are fundamentally without scientific merit. The issue in the application was quite an error on it. This was the examiner's 's reason for allowance: The prior art does not show nor fairly suggest the method of treating the

particular condition (ADHD) with an effective amount of a particular drug tomoxetine. That was the issue. And frankly, the question of whether some other drug might have been used for that purpose is really irrelevant.

And the fact of the matter is that this tandamine reference did not suggest that even it should be used for ADHD, and Dr. Berridge testified on cross-examination, and we expect he will do the same in this Court:

"QUESTION: Would the tandamine reference have any bearing on the central issue of the obviousness of the '590 patent?

"ANSWER: I don't think so."

It was fundamentally technologically relevant.

And the same is true of this urinary incontinence point. Urinary incontinence is a peripheral effect, fundamentally different from the complex interactions, the goings-on inside the brain that we spent so much time talking about.

Again, with Dr. Berridge:

"QUESTION: Have you formed any opinion as to whether the urinary incontinence information you cite would have been material to or relevant to the examiner considering whether to allow the '590 patent ?

"ANSWER: No. I don't believe it would have been relevant."

And that's to say nothing, Your Honor, of the complete absence of evidence of any kind of intent to deceive. And the law is quite clear here, the Star Scientific case, the inference of intent to deceive has to be the single most reasonable inference to be drawn from the evidence, and they have not come close to that.

On the tandamine reference, I think the Court denied summary judgment because it thought we had submitted that reference in other cases. The evidence will show we did not.

Now, the enablement analysis.

This argument, Your Honor, is completely without precedent and if it were accepted could be applied to virtually ever pharmaceutical patent based on the discovery of new therapeutic use.

The invention is not a dosage form, and very much unlike the Alza case, where the invention was using a particular dosage form.

Here, the invention was the discovery that tomoxetine has this therapeutic effect when administered to this class of patients, and that's what the patent is all about. Alza required a specific kind of dosage form and they had failed to disclose how to make it. It has nothing whatsoever to do with this case.

If I can go back to that for just a minute, they

say, Oh, but it covers doing it anyway.

Of course it covers doing it anyway. It covers people who discover new ways of doing it 10 years from now, eight years from now, whenever the patent expires. That's in the nature of patents. The fact that it wouldn't be infringed by this claim does not mean that all of a sudden the claim is invalid because we didn't disclose all of these potential future dosage forms. The question is, could somebody practice that invention without undue experimentation?

We think the answer is yes. One hundred percent of the ADHD market at the time this patent application was filed was all immediate and sustained release tablets and capsules.

They concede, Your Honor, as they must, that this patent specification is completely enabling for tablets, capsules, or oral dosage forms like that, and, indeed, the patent says, since it's orally administered, why you would rarely if ever use it any other way.

And as to sustained release tablets, those are in the prior art, Your Honor. There's a patent, this '092 patent, Plaintiff's Trial Exhibit 72, it's an invention on sustained release pharmaceutical compositions, and example 4 is an example with tomoxetine hydrochloride.

Patents are not production specifications. I can

cite you 15 cases that say that. That which is known to those of ordinary skill in the art need not be disclosed and is preferably omitted. I can cite a dozen cases that say that. And what they're asking is that we take an industrial manufacturing specification and append it to the patent application for every conceivable dosage form somebody might want to use and every conceivable salt form, and on failure to do that, the patent is invalid. And that's simply not the law.

The patent says, all it says, use the usual dosage forms. People of ordinary skill in the art know what those are.

On other pharmaceutical forms, use those that are well known to and understood by pharmaceutical scientists.

What does that mean?

There are textbooks, Your Honor, that are devoted to this topic. It is a standard part of the pharmaceutical business that everybody in it goes through. This is just one example, Plaintiff's Trial Exhibit 543, and you can look down the list and see that it instructs you how to make all of these various dosage forms.

Moreover, there's prior art. There's this Canadian patent, Plaintiff's Trial Exhibit 473, which describes how to make oral and liquid dosage forms of tomoxetine. That patent also describes other forms, like

subcutaneously administered ones or sublingual disks or suppositories. That's all in the prior art.

What is the dispositive factor? The dispositive factor is that the evidence will show that there was nothing about the properties of tomoxetine that made it in any way troublesome or problematic for people to formulate as they saw fit. It was regularly used as a salt.

Keep in mind, Your Honor, this patent is not about a new drug. Tomoxetine had been disclosed in the prior art. It had been the subject of clinical trials for depression, which, by the way, failed. It was a well-known actual material that had been formulated already into pharmaceutical dosage forms. It was notably safe, it was readily orally available, it was crystalline, it was stable, it was soluble, it had previously been formulated. There is nothing to indicate that a person of ordinary skill in the art could not, doing what pharmaceutical formulators do every day, make and use the method of treatment invention which is the subject of the patent.

Thank you very much, Your Honor.

THE COURT: Thank you.

Who's going to be the first witness?

MR. ROCKEY: Your Honor, Keith Rockey for Sandoz. The first witness will be Dr. Craig Berridge.

THE COURT: All right, and how long will he be?

MR. ROCKEY: About, roughly two hours, two and a half max.

THE COURT: Okay. It's almost 10:30. Do you want to take a short break and then we'll bring him in?

MR. ROCKEY: Fine.

THE COURT: All right. Why don't we just take about 10 minutes?

(Recess taken)

THE COURT CLERK: Remain seated.

THE COURT: Be seated.

All right. Let's call our first witness.

MR. ROCKEY: Thank you, Your Honor.

Defendants called Dr. Craig Berridge.

THE COURT CLERK: Placing your left hand on the bible and raising your right hand:

C R A I G B E R R I D G E, called as a witness on behalf of the Defendants, and having been duly sworn, testified as follows:

THE COURT CLERK: Please be seated.

Please state your name, spelling it for the record.

THE WITNESS: Craig Berridge, C-r-a-i-g, B-e-r-r-i-d-g-e.

MR. ROCKEY: Thank you, Your Honor.

DIRECT EXAMINATION

BY MR. ROCKEY:

Q. Dr. Berridge, would you state for the record your name and current home address, please?

A. Craig Berridge, 2217 Rowley Avenue, R-o-w-l-e-y, Madison, Wisconsin.

Q. And by whom are you employed?

A. The University of Wisconsin, Madison.

Q. What is your position at the University of Wisconsin?

A. I'm a -- my primary appointment is in psychology. I'm a professor in psychology, and I have an affiliative appointment in psychiatry.

Q. How long have you been on the faculty at the University of Wisconsin?

A. Nearly 15 years.

Q. Would you describe the positions you've held on the faculty at Wisconsin?

A. I began as an assistant professor in the Psychology Department. I was promoted to associate professor, and then I was promoted to full professor.

Q. Would you describe previous positions that you've held prior to coming to Wisconsin?

A. I was a -- after, following graduate school in neuroscience at the University of Florida, I held a couple of postdoctoral research positions, one at the University of

California San Diego in their Psychiatry Department, and one was at Yale University Medical School in the Pharmacology Department.

Q. Would you describe your educational background?

A. I have a Bachelor's of Art degree from the University of California San Diego in psychology as well as biochemistry and cell biology.

Q. When was that degree awarded?

A. That was in March of 1982.

Q. Any advanced training beyond that?

A. I received my doctorate in neuroscience from the Medical School at the University of Florida.

Q. And when was that degree awarded?

A. That was in December of 1988.

Q. Can you tell us what neuroscience is?

A. Neuroscience is the study of nervous systems, and because a key part of nervous systems is the neuron, much of neuroscience focuses on the biology and functions of neurons.

Q. And what is your specialty in the field of neuroscience?

A. I have a broad specialty in behavioral neuroscience, and more specifically, I have specialty in the behavioral actions of neurotransmitter systems, and then if we get more specific, I have expertise in a type of neurotransmitter

class called the catecholamines, and the catecholamines for brain function, the two that are largely the focus of study are norepinephrine and dopamine.

MR. ROCKEY: Your Honor, we'll be getting into those details in a few minutes.

Q. Have you in the course of your work used drugs in your studies?

A. We use drugs extensively to manipulate neurotransmitter systems and different aspects of neurotransmitter function, so yes.

Q. Okay. Does that include ADHD?

A. That includes drugs that are commonly used in ADHD, yes.

MR. ROCKEY: Your Honor, I've handed to the witness and to opposing counsel as well as your clerk a series of notebooks of exhibits. The first one I'm going to start off with --

THE COURT: Does my law clerk have one?

MR. ROCKEY: Oh, I guess the witness needs it, yes.

THE COURT: For what it's worth, anybody that is going to be handing me anything, it's more important that my law clerk has it.

(Laughter)

MR. ROCKEY: A question, Your Honor, of procedure,

how you prefer to proceed. Are we to assume that any exhibit not objected to is received in evidence, marked in the pretrial order?

THE COURT: How do you want to proceed? There's no jury here, so I'm not as concerned about poisoning someone's mind because they see something that they shouldn't see.

I will do whatever facilitates and make your presentations simpler. I assume you know what's going to be objected to. In all likelihood, if there's no objection to something, I am probably not going to sui sponte find an objection.

MR. LIPSEY: Just for purposes of good order, I think it would be helpful as we go through them, since you may not use all of the exhibits in the book, if you were to offer them, and if we have no objection, we'll state we have no objection.

THE COURT: Okay.

MR. LIPSEY: If that's all right.

THE COURT: I guess that would probably keep the record clear. Why don't we try it that way to move it quickly?

MR. ROCKEY: Okay. And one other question, Your Honor, related to that, and that is that we will in the course of Dr. Berridge's examination, as you look through

the notebook, be marking some forensic charts, which are demonstrative exhibits. Does Your Honor prefer that those be marked as exhibits, or just submitted to the Court at the close of the trial?

THE COURT: Well, if you're going to refer to them, they should probably be marked as exhibits, again, for clarity of the record.

MR. ROCKEY: That's fine.

THE COURT: And again, if they're not into evidence, they're just going to be for demonstrative purposes, let that be known, and we'll deal with it accordingly.

MR. ROCKEY: Okay. Very good.

BY MR. ROCKEY:

Q. Dr. Berridge, have you found Exhibit 47 in your notebook?

A. Can you repeat which exhibit that is?

Q. Yes. Look in the notebook for Defendants' Trial Exhibit DTX-47.

A. Okay. Forty-seven. Yes.

Q. Did you find it?

A. I did.

Q. Okay. Is that your CV?

A. Yes.

THE COURT: Is there going to be any objection to

offering this witness as an expert in the field of I guess neuroscience?

MR. LIPSEY: Your Honor, our objections really go more to the weight of his testimony. We'll bring it out on cross.

THE COURT: You can deal with that on cross-examination. But as far as offering him as an expert, since I'm going to have the benefit of his curriculum vitae, I don't think it's necessary to go through the doctor's background as we normally would in front of a jury.

MR. ROCKEY: That's fine with me, Your Honor.

MR. LIPSEY: I mean, I hate to suggest it, but it might be important, the distinction between the qualifications of the two experts.

THE COURT: All right. Then go ahead.

MR. LIPSEY: And I would have no objection to going through it; but of course, you're the judge.

THE COURT: Counsel, by the way, when I ask for something that might in my view be more efficient or quick, if you believe that in any way it's going to harm your position, don't be afraid to say so. I'll be okay with that. So go ahead. Go through them.

MR. ROCKEY: So the consensus is I should continue.

THE COURT: I think that's the consensus.

MR. ROCKEY: Well, I don't agree, but I'll certainly do it that way.

(Laughter)

BY MR. ROCKEY:

Q. Have you prepared any publications and made any presentations, Dr. Berridge?

A. In the course of my career, I've prepared a number of publications and a number of presentations related to my research in neurotransmitter function, with a heavy emphasis on catecholamines, and in particular, norepinephrine.

Q. Yes. I'd like for you to just summarize, I don't think we need to go through a whole extended list, but would you summarize generally the subject matter, the publications and presentations that you've made?

A. They're focused on what are the behavior -- there are a couple of questions. They're focused on what are the behavioral functions of norepinephrine, and that takes place in the context of stress and arousal, and then they're focused on the neurobiology of the psychostimulants, drugs that are widely used in ADHD, and what their biological and neurochemical actions are. And that's in the context of how these stimulants promote arousal, and then more recently, how do stimulants enhance cognition, which would be relevant to their therapeutic effects in ADHD.

Q. Have you ever served as a consultant to the

pharmaceutical industry?

A. I have served on a number of instances, occasions.

Q. Can you briefly summarize the kinds of activities you've undertaken as a consultant in the pharmaceutical industry?

A. Right. My activities have taken three forms. In the first, I've tested compounds that have been identified by drug discovery programs and tested them as far as their behavioral or neurochemical actions.

In the second form, I have attended scientific advisory boards of pharmaceutical companies that are focused on ADHD medications, and there, we discussed what is known about the known, the current drugs that are used to treat ADHD, specifically psychostimulants or alpha-2 agonists.

In the third capacity, I've facilitated, assisted in-house in pharmaceutical drug discovery programs in their development of an animal research program that would allow them to test the behavioral actions of an identified compound.

Q. Do you distinguish between drug discovery and drug development?

A. I do, and I think most people do. Drug discovery is the identification of compounds that might have clinical potential, and drug development is the taking of those compounds and determining clinical uses.

Q. Very good.

Have you received any grants from anybody?

A. In the course of my career, I've received a number of grants, thankfully, and these are from the National Institutes of Health, both the National Institute of Mental Health and National Institute of Drug Abuse, as well as the National Science Foundation.

Q. Over what kind of time period are we talking about?

A. Since my graduate school, the start of graduate school, and then certainly during the course of my time at the University of Wisconsin.

Q. Do you carry a teaching load at the University of Wisconsin?

A. I do. I teach at both the undergraduate and graduate levels.

Q. What do you teach?

A. These days it's primarily neuropharmacology, the study of drugs that affect brain function, and that's both at an undergraduate class or level and a graduate level, and then early in my tenure there, I taught behavioral neuroscience to undergraduates.

Q. And what kind of behavioral neuroscience have you taught?

A. Well, at the behavioral neuroscience one, that was a course that I taught. It was simply the topic of behavioral

neuroscience, which is how does the brain control behavior across a wide range of functions. In my neuropharmacology course, it's what do the neurotransmitter systems do behaviorally and what drugs do to these neurotransmitter systems, and in the treatment of how do drugs used in the treatment of psychiatric disorders, how do they affect brain activity, pharmacologically, what do they do.

Q. Have you had any teaching responsibilities in the field of ADHD?

A. In my neuropharmacology courses, both in the undergraduate and graduate, we have a -- I have a section where we talk about psychiatric disorders and drugs that are used to treat them, and one of the disorders we talk about is ADHD.

Q. Have you been an invited speaker at any meetings that deal with ADHD, Dr. Berridge?

A. I've been an invited speaker at a number of meetings that have focused on the pharmacology of ADHD.

MR. ROCKEY: Your Honor, at this point, I would offer him as an expert in neuroscience.

MR. LIPSEY: No objection with the proviso I noted.

THE COURT: With the proviso what?

MR. LIPSEY: I noted, which is, our objections will go to the weight to be given his testimony. We'll deal

with them on cross.

THE COURT: I don't think that's a proper basis for objecting to an expert. I'll certainly allow you your opportunity to cross-examine.

I'll allow this witness, Dr. Berridge, to testify as an expert in the field of -- I guess it's neuroscience?

MR. ROCKEY: Neuroscience, Your Honor, yes.

BY MR. ROCKEY:

Q. Okay. Let's go to the first slide.

Dr. Berridge, have you had occasion -- or the second slide -- have you had occasion to look at the '590 patent that's involved in this lawsuit?

A. I have.

THE WITNESS: Can I just add one thing to that last conversation you two had?

THE COURT: Which conversation?

THE WITNESS: Well, my expertise. I would say it is in neuroscience, and then more specifically, it's in neuropharmacology.

THE COURT: Okay.

THE WITNESS: I don't know if that's relevant, but that's more precise.

THE COURT: Okay.

MR. ROCKEY: Thank you, Your Honor.

A. Yes, I have had a chance to look at the patent.

Q. Okay. Can you briefly describe what you understand the '590 patent to be directed to?

A. This patent describes the method for treating ADHD with a compound called tomoxetine, which we'll be referring to as atomoxetine.

Q. What is atomoxetine?

A. Atomoxetine is a drug that has a specific pharmacological action, and that action is, it blocks norepinephrine reuptake.

MR. ROCKEY: Incidentally, Your Honor, I don't think there is any dispute about this. Tomoxetine was the older name. Now it's more frequently identified as atomoxetine --

THE COURT: Okay.

MR. ROCKEY: -- as a result of some FDA issues.

THE COURT: No one wants to make it simple.

(Laughter)

MR. ROCKEY: Well, apparently it was being confused with the breast cancer drug tomoxaphine (ph). And so the FDA said why don't you call it atomoxetine.

THE COURT: All right.

BY MR. ROCKEY:

Q. Now, is atomoxetine a new compound?

A. Atomoxetine is not a new compound. I think it was described in the early 80's or late 70's.

Q. Now, in your review of the patent, did you find any data to show whether and to what extent atomoxetine was effective in the treatment of ADHD?

A. I saw no data that showed that atomoxetine is effective in the treatment of ADHD.

Q. Okay. Now, let's get into the background of neuroscience, if we might, a little bit.

You describe neuroscience as the study of neurons and how they behave. We should start, perhaps, with the question of what is a neuron.

MR. ROCKEY: Put the next slide up.

Q. What is a neuron?

A. Well, as shown in this schematic, and it's highly simplified, but it's accurate for today's purpose, a neuron is a specialized type of cell that -- what makes it unique is that it's electrically excitable, and neurons talk to each other via neurochemicals, called transmitters or neurotransmitters, and this just shows some of the anatomy of a neuron. There's a cell body, there's a thin extension or cable that's called an axon, and then that axon ends in a specialized ending called a terminal.

Q. How do neurons function in general terms?

A. How do they -- well, they function in general terms by communicating to each other, and that involves the release of these communicating chemicals called neurotransmitters.

Q. Okay. Let's go to the next slide, if we might.

What do we have up on the screen there, Dr. Berridge?

A. Well, we have -- there's a lot of things on the screen, and I'll try to walk through them quickly but clearly.

We have -- just on the left here are two neurons, and this top one is talking to this bottom one, and the place where it talks is called a synapse. In this, when we talk about two neurons talking to each other, we refer to the presynaptic neuron as the one talking, releasing the neurotransmitter, and we refer to the postsynaptic neuron as the one receiving that information in the form of a neurotransmitter. And then that specialized, where all the work happens is this specialized connection called the synapse, and that's blown up over here. And in this --

Q. Okay. Well, we'll get into that in a second.

MR. ROCKEY: Your Honor, I think we're going to have to mark these as exhibits. I think it would be more efficient if we marked it at the end of the examination and offered it, but I can do it now. I hate to take up trial time to be marking exhibits.

THE COURT: Well, aren't these premarked?

MR. ROCKEY: Not the slides, Your Honor.

THE COURT: Because these were the ones you're

going to use -- are you going to be offering these into evidence?

MR. ROCKEY: Yes.

THE COURT: Are there any objections to any of these slides?

MR. LIPSEY: No, Your Honor. My suggestion would be to mark the book, perhaps, as Defendants' Demonstrative Exhibit 1 and then use the slide numbers as parenthetical subnumbers.

THE COURT: Are there going to be any objections to anything else in the book?

MR. LIPSEY: My review of it last night led me to believe no, Your Honor.

THE COURT: All right. Then what we'll do, we'll mark this book for the moment -- I don't know how your markings have been. How do you want to mark it?

MR. ROCKEY: Defendants' Trial Exhibit Number: The next one is 553, Your Honor, DTX-553.

THE COURT: All right. We'll mark the book DTX-553 and that will come into evidence thereafter and we'll mark with an evidence marking. Go ahead.

MR. ROCKEY: Perfect.

THE COURT: And then at the end of the testimony, you can put forth that which you believe after counsel has looked at it what will be marked into evidence.

MR. ROCKEY: Thank you, Your Honor.

(Defendants' Trial Exhibit 553 marked for identification)

BY MR. ROCKEY:

Q. Okay. We talked about the left-hand side of slide 4 of Exhibit 553, Dr. Berridge. Can you tell us what the right side of the drawing is?

A. Right. That's a blowup of this specialized synapse, and it shows the major components involved in neurotransmitter action in neurotransmission.

Q. Okay. Now, we look at that, and we see a notation, "Terminal." How does -- where does that compare or what -- how does that correspond with the neuron?

A. So --

Q. Can we go back to the neuron for a second? Yes, that's it.

A. So the terminal is the specialized ending called the axon terminal, and that's where neurotransmitters are being released from.

MR. ROCKEY: Okay. Let's go back to slide 4, if you would, please, Jeff.

Q. All right. Now, we see the note "Neurotransmitter." What does that mean?

A. So neurotransmitters are chemicals that are secreted by a neuron or released by a neuron, and then they travel

across this space, this synaptic space and bind to specialized proteins, called receptors. And when it binds, that means to physically attach. When it physically attaches to the receptor, that initiates a biochemical signal in this postsynaptic neuron, which is that one over here, and that biochemical signal changes the activity of that postsynaptic neuron. In some way, it's providing information to that neuron.

Q. Okay. Now, we have some other terms we need to define on slide 4, Dr. Berridge.

You've told us about neurotransmitter.

Vesicles: What's that?

A. The vesicles -- the neurotransmitters are packaged and they're sitting there waiting to be released, and the way they're released is, they're stored in vesicles, and that's again just a storage form for the neurotransmitter, and then that vesicle moves, physically moves over to this part of the terminal and spills out its contents of neurotransmitters into that space.

Q. Okay. We also see a presynaptic receptor in yellow. What's that?

A. Right. As if it isn't complicated enough, we have receptors on the postsynaptic neuron, and they're involved in the communication between these two neurons, but neurons can also have a receptor on the terminal, on the presynaptic

neuron that binds, interacts with this transmitter that is being released. So as an example, if this is norepinephrine, because we will get there, then norepinephrine will be released and it will bind to a norepinephrine receptor that sits here, and the function of that is to provide a negative feedback signal. It dampens the amount of release that's going on, and it's similar, the example I typically give is it's similar to a thermostat on a furnace. So the furnace goes up in temperature to some point, and then the house thermostat shuts -- slows down the rate of heat output. And that's what these things are doing. These presynaptic receptors are keeping release within a more narrow range than you would have if you didn't have those presynaptic receptors.

Q. Now, we also see in slide four of Exhibit 553 three -- I'm not very good at colors -- rust-colored things labeled "Reuptake Sites." What are those?

A. Once the transmitter is released and it sends a signal to the adjacent neurons, it's important that that signal is eventually stopped, that the transmitter doesn't sit around indefinitely, and there are two ways that that can happen. You could have enzymes out in the synaptic cleft which break down the transmitter, but in the case of the catecholamines, monoamine transmitters that we'll be talking about today, the primary way that those transmitters are inactivated is

that they're suctioned out of this space, vacuumed up by these specialized proteins, which are referred to as reuptake sites.

Q. What happens if a receptor comes into contact with a reuptake site?

A. Receptors typically don't come into contact with reuptake sites.

Q. I misspoke. Sorry.

What happens when a neurotransmitter comes into contact with a reuptake site?

A. So there's a physical binding to it, just as with the receptors, but in this case, instead of signaling some signal inside, that reuptake site physically takes that transmitter and puts it into this terminal, sends it back into the terminal from which it was released.

Q. Okay. In slide four, we also see a rectangular shape, looks a little yellowish to me, called enzymes. What's that?

A. Once the transmitter is taken back into the terminal by these reuptake sites, it can take one of two paths. It can go back into the vesicles for later release so the transmitters can be recycled, or it can be enzymatically degraded, and that's what this schematic indicates, that there are enzymes that are in the terminal that can degrade transmitters. And the more that they degrade transmitters,

the less there is for repackaging and release.
Q. Now, what neurotransmitters are relevant here to this case in dealing with ADHD?
A. We're going to -- when you talk about the pharmacology of ADHD, and certainly in this case one will talk about generally a class of transmitters called monoamines, referring to the fact that they have a single amine group, not to get technical, but that's a nitrogen atom with a couple of hydrogens, and then you can break out the monoamines into different categories. Monoamines include serotonin, which is called an indolamine, and then it includes catecholamines, and specifically, those are norepinephrine and dopamine.
Q. And each of these, norepinephrine, dopamine and serotonin, are neurotransmitters?
A. They're all neurotransmitters. They're structurally different. They bind to different receptors.
Q. Okay.
A. They're released from different neurons.
Q. Okay. Which neurotransmitter do you think is the most important when it comes to ADHD?
A. Well, I'll tell you, there are multiple ways to look at that question, but the short answer is, I -- there's -- no one knows what the most important neurotransmitter is when it comes to treating ADHD.

Q. Which are the ones that are talked about the most?
A. The ones that are talked about and that are certainly affected by drugs that treat ADHD are the catecholamines, dopamine and norepinephrine.
Q. Okay. Let's talk about norepinephrine specifically.
MR. ROCKEY: And if we go to slide 5, please, Jeff.
Q. Okay. Can you tell us what we're seeing here in slide 5 of Exhibit 553, Dr. Berridge?
A. So this is very -- this is a similar organization to the schematic that we were just looking at that was for a generic neuron. This is for a norepinephrine neuron. So instead of saying transmitters over here generically, they're labeled as norepinephrine. This is a norepinephrine terminal. We'll be abbreviating probably on some slides norepinephrine as NE.
Norepinephrine is in vesicles, indicated by these blue circles. These are different norepinephrine receptors on a postsynaptic neuron, and there are three major classes of receptors, and they're labeled alpha-1, alpha-2, and beta. And then there are presynaptic receptors, and those turn out to be alpha-2 receptors, and they're similar structurally to the postsynaptic alpha-2 receptors.
Q. Now, the other terms that appears for the first time there in slide 5 is the term "Monoamine" and "Oxidase."

A. Right.
Q. What's that?
A. So that is an enzyme, just as it was labeled in the previous schematic. Monoamine oxidase is an enzyme. It's found in monoamine terminals, including norepinephrine, but that would also include serotonin and dopamine, and it serves a degradative function. It takes the transmitter and degrades it.
Q. Is that important?
A. Evidently, it is important. We don't really know what the function is for brain function, but we know that when norepinephrine is degraded by this enzyme, there is less for repackaging and rerelease.
Q. Now, you've described the different norepinephrine receptors. How do they differ from each other in the sense of what happens in a neuron?
A. Right.

So they're different structurally, they're different proteins. They all bind norepinephrine, so they have that in common. But what's different is that when norepinephrine binds to this receptor, physically attaches to that receptor, each receptor sends a different biochemical signal to that postsynaptic neuron, and though the functions of those signals aren't entirely known, but we certainly know that those are different signals, and that

allows this neuron or different neurons to keep track of which receptor is being stimulated.

Q. Okay. I think we've defined all the terms there. Let's move on.

How does neurotransmission work, and have you prepared anything that would illustrate that?

A. So we have an animation that goes over this general principle. Before we go there, I'll just point out that there are these norepinephrine reuptake sites, they're the generic reuptake site that was in the other neuron. In this case, they're specific for norepinephrine. They won't take up other neurotransmitters in general.

Q. Okay. Thank you. I omitted that.

Okay. Let's go on to slide 6.

A. All right. So we're going to see is just an animation, and it's a complicated process, and I think the animation adds some clarity to that process. We're going to see norepinephrine being released. It's going to bind to different receptors. When it does, there's going to be a response, a physiological response in the two different parts of this synapse, the presynaptic terminal and the postsynaptic neuron, and then after it does that, it's going to get taken up, and then it can either get degraded or it can go back into the vesicles for later release.

Q. Okay. Let's start the animation.

And when you get into it, if you pause it --

A. So there's norepinephrine being released.

Can you pause it there?

And it's binding to receptors, and it could be an alpha-1 or an alpha-2 or a beta receptor, and here, the norepinephrine molecule is going up to the alpha-2 presynaptic receptor, and when it binds, it produces a physiological response, and we're indicating that by having it light up. Okay?

Q. Okay.

(The animation continues)

A. And then it's going to get cleared up by the reuptake sites, and it's going to get repackaged or it's going do get degraded by this monoamine oxidase enzyme, and that just continues. You get more release, more responses, taken up, repackaged, degraded by monoamine oxidase.

Q. Okay. Now, that light flashing is symbolic of what, Dr. Berridge?

A. The neurotransmitter having an effect on the physiology of this neuron.

Q. Okay. Very good.

THE WITNESS: Mr. Rockey, do we have a sheet that defines a lot of these terms or abbreviations?

MR. ROCKEY: Oh, we do. I forgot about that. Thank you.

We do have a sheet that's in the book, I believe, of definitions.

THE WITNESS: There is a lot of terms, and one can get lost in the terms.

MR. ROCKEY: That's a glossary of the terms that Dr. Berridge has already defined.

Okay. Let's go on, Dr. Berridge.

Thank you, Eric.

Q. How do drugs -- well, go back to ADHD. What classes of drugs have been used, let's say before January of 1995, in the treatment of ADHD?

A. There are four main classes that people typically have talked about and studied and used in the treatment of ADHD. There are more, but there are what I believe are four main classes, and they target, interestingly, they target different aspects of this neurotransmission process. And by far, the most effective drugs out there, of course, the psychostimulants are widely acknowledged as being the most effective drugs are the psychostimulants. Psychostimulants act pharmacologically by blocking norepinephrine reuptake, so they would physically interact with this reuptake site and prevent norepinephrine from getting in there. That will increase the amount of norepinephrine floating around.

They also -- similarly, they block dopamine reuptake, another catecholamine, another neurotransmitter,

and in the same way, they will increase the levels of dopamine in the synapse, and the amount of dopamine available for signaling or communicating to other neurons.

A second class of drugs that's been commonly used and studied, not everyone responds well to the psychostimulants or there are some patients where symptoms would contraindicate the use of psychostimulants, so there is another category of drugs that everybody used. Those are the tricyclic antidepressants. And the tricyclic antidepressants share in some manner the pharmacological actions of the psychostimulants. They also block the reuptake of monoamines. In this case, norepinephrine and serotonin are the two transmitters that get targeted most predominantly and are most frequently discussed, but they can also affect dopamine. So as a class, they're called monoamine reuptake blockers.

A third class of drug is the alpha-2 agonist.

Q. What is an agonist?

A. The terms keep going on.

An agonist is a drug that mimics the activity of the internal transmitter. So in this case, an agonist will bind to this receptor, this alpha-2 receptor, it's an alpha-2 agonist, stimulate that receptor, produce the biochemical response that that receptor drives. And that, of course, will occur at both the postsynaptic and

presynaptic alpha-2 receptors.

And then lastly, the other class of drugs, though in the United States these are not typically used as a second-choice drug, they are the monoamine oxidase inhibitors, and they'll be abbreviated as MAOI. That's shown on that board. And what they do is, they block the activity of this enzyme, and when you block the activity of that enzyme, you increase the amount of transmitter available for release, and this would include norepinephrine, serotonin, and dopamine.

So one thing all these drugs have in common is they in one way or another influence monoamine neurotransmission.

Q. Okay. Mentioned four. What's the other one?

A. I think I covered four. Monoamine oxidase inhibitor was four. We have monoamine oxidase inhibitors, alpha-2 agonists, tricyclic antidepressants, and psychostimulants.

Q. Which of these groups do you believe have been most intensely studied in the literature?

A. Well, by far, the most intensely studied because they're the most effective and the most widely used are the psychostimulants.

Q. Okay. What's number two, if you rank them?

A. Well, my understanding of the reading of the literature, the next most intensively studied would be the

tricyclic antidepressants.

Q. Okay, and what do the tricyclic antidepressants do?

A. Pharmacologically or behaviorally or --

Q. Pharmacologically.

A. The tricyclic antidepressants as a class block monoamine reuptake, and typically the two monoamines that they tend to target most strongly are norepinephrine and serotonin.

Q. Okay. Would you go to the next slide, please?

Okay. Tell us what we have here in slide 8, I guess it is.

A. This is just a schematic. It's -- again, we're focusing on a norepinephrine terminal, and what we're going to see is how a reuptake blocker would influence or affect the level of norepinephrine in the synapse and the amount of receptor frequency that would be driven by that.

This, for the tricyclics, will affect norepinephrine reuptake, but as I said, they'll affect others, perhaps, and then again the psychostimulants, one common action of those or one action of the psychostimulants is they also block norepinephrine reuptake.

All right. So can you pause it there?

So this is just the reuptake blocker. The norepinephrine reuptake blocker simply does what its name says: It blocks norepinephrine reuptake. And to do this,

it has to physically bind or interact with the reuptake site. Okay?

So you get norepinephrine release. You get norepinephrine receptor action. But now norepinephrine can't be taken back up, sucked up, and so you get an accumulation of norepinephrine, and that's going to lead to greater signaling at both the postsynaptic and presynaptic receptors.

Q. What are the green triangles?

A. The green triangles are just identifying a norepinephrine reuptake blocker blocking norepinephrine.

Q. And are green triangles known in the real world specifically?

A. Are there norepinephrine reuptake blockers?

Q. Yes.

A. There are. As I said, the psychostimulants do this, and then as a class, the tricyclic antidepressants do this.

Q. Okay.

A. There are also selective -- there are selective norepinephrine reuptake inhibitors as well.

Q. Okay. Any other --

A. And then, of course, and atomoxetine is a norepinephrine reuptake blocker, and so this would indicate how atomoxetine in a schematic form is going to influence norepinephrine.

Q. Okay. So if you were to compare on the basis of this slide how desipramine, for example, as a member of the tricyclics and atomoxetine work, would there be any difference that you could see on the --

A. In terms of their ability to block norepinephrine reuptake, no. They could -- that's their -- that's how we describe a pharmacological action. When we say pharmacological action, we mean, what is that drug physically interacting with and influencing at the neuron level? After that, it gets complicated very quickly, but that's the pharmacological action of the desipramine and atomoxetine when we're talking about the norepinephrine reuptake site.

Q. Have you formed any opinions as to whether a person skilled in the art -- well, we need to talk about that for a moment, because we haven't.

Have you formed an opinion as to whether one skilled in the art would have found it obvious in 1995 to use atomoxetine in the treatment of ADHD?

THE COURT: Do we have a definition of what one skilled in the art is?

MR. ROCKEY: Yes, we are, Your Honor, and that's what's next.

THE COURT: Shouldn't we know that before the question?

MR. ROCKEY: Dr. Berridge has gone through the three Graham factors. The first is on slide 10, and on the left-hand side, Dr. Berridge's definition; on the right-hand side, the definition of Plaintiff's expert, Dr. Pliszka.

Q. How, do you find much difference between those two views on level of skill?

A. No, I find little difference. We both suggest or state that advanced training in the form of a Ph.D. or M.D. degree would be necessary, and then there would have to be additional expertise and training, postgraduate training in the use of drugs that influence behavior in psychiatric disorders.

Q. So you're in general in agreement with Dr. Pliszka?

A. That's correct.

Q. Looking at slide 11.

The second of the Graham factors, did you look at the scope and content of the prior art, Dr. Berridge?

A. I did.

Q. And what did you find in the prior art?

A. That the prior art teaches that a norepinephrine reuptake blocker is effective in the treatment of ADHD, and primarily, the most intensively studied example of that is desipramine, and that though desipramine has other actions, those are linked to side effects, and atomoxetine not having those other actions would be effective in the treatment of

ADHD without having those side effects.

MR. ROCKEY: Okay. Let's go to the next slide, 12.

Q. Now, Mr. Clement used this.

Have you looked at the Donnelly publication, Donnelly et al publication?

A. I have. I did.

Q. Who are the authors?

A. So the first author is Maureen Donnelly. This actually is a group at the National Institutes of Health, National Institute of Mental Health in the child psychiatry branch, I believe. Maureen Donnelly -- it consists of the first author, Maureen Donnelly, but other author include Alan Zametkin and Judith Rapoport.

Q. What does the Donnelly et al publication talk about?

A. It talks about how one of the tricyclic antidepressants, desipramine, is effective in the treatment of ADHD, and they do this in a double-blind clinical study looking at desipramine's effects in children with ADHD.

Q. Let me stop you here because somebody whispered in my ear that the level of skill might not be as clear as it might be.

Let's go back to that slide 9 -- 10. Ten is what I want. Okay.

Now, your view is Ph.D., M.D., training --

A. Training in neurotransmitters and neurotransmitter action. I think if you're going to talk about pharmacology of ADHD, you're going to have to be familiar with catecholamines and monoamines, and then additional training after your graduate training.

Q. Okay.

A. And Dr. Pliszka suggests expertise in pharmaceutical chemistry or psychiatry with an M.D. or Ph.D. degree, and three to five years in experience in development in clinical use of drugs and therapies for psychological disorders. And if you're going to talk about drugs for psychological disorders, you're going to have to talk about monoamines and the drugs that influence those.

MR. ROCKEY: Okay. Let's go back to slide 12.

Q. Now, we were talking about the Donnelly et al publication. And you mentioned double-blind study. What is a double-blind study, and what's it got to do with anything?

A. A double-blind study is considered the most rigorous way to test the clinical effects of a drug, and the double-blind phrase refers to the fact that both the patient, the person receiving the drug, and the person prescribing the drug or scoring the behavioral effect or clinical effect of the drug, the person participating directly in the study, do not know what the person -- the patient is receiving, whether they're getting the drug or a

control, placebo control type compound. So they're both blind, the patient and the investigator are blind to the experimental treatment that an individual is getting.

Q. And that's good?

A. That's considered the most objective and rigorous way to determine whether there's a behavioral action of the drug.

Q. Okay. Now, we see in the excerpts from the first page of Donnelly -- well, first of all, what was Donnelly using to treat ADHD?

A. So in this study, as I said, they're using desipramine, and it's common to abbreviate it as DMI. Those are some of the initials that are in the longer chemical name of it, but it's frequently referred to as desipramine. And they show that there's a clinical and immediate effect of desipramine in the treatment of ADHD.

Q. Okay. Now, in the second portion of the first page there, there is a reference to noradrenergic mechanism. What is that?

A. Well, what they're suggesting, and I'll explain this a little bit in a second or two, what they're suggesting is that the ability of desipramine to improve ADHD symptoms relates to an influence, a reuptake blocking action on norepinephrine, and it's even more complicated: Norepinephrine and noradrenergic are synonymous. The

British called norepinephrine noradrenaline, and we call norepinephrine norepinephrine. So they're synonymous.

Q. So they mean the same thing?

A. They mean the same thing. So when they say a noradrenergic mechanism, they're saying a norepinephrine mechanism.

Q. Saying what?

A. They're saying an norepinephrine mechanism.

Q. Okay. Now, let's go on to the next page.

MR. ROCKEY: Incidentally, Your Honor, this is Defendants' Trial Exhibit 23.

Go on to slide 13, if you would.

Q. Now, there's another quotation singled out there, actually two of them. It referred at the beginning to imipramine.

What is imipramine?

A. Well, this is -- this paragraph is where they get -- where they reach the conclusion that there's a norepinephrine mechanism underlying desipramine's clinical effects, and the tricyclics as a group had been shown to be effective in treating ADHD. That had been known for a number of years. A commonly used tricyclic antidepressant, both in the treatment of depression and ADHD, had been imipramine, and as I said, as a class, the tricyclics block monoamine reuptake, particularly blocking norepinephrine and

serotonin, and that's true of imipramine.

Desipramine, it's always been interesting that desipramine doesn't block serotonin reuptake in any appreciable way, and thus it is more selective, it's a selective norepinephrine reuptake blocker when we compare it to the other tricyclic compounds. And so what they're saying is, in contrast to imipramine, desipramine has relatively specific neuropharmacological action on transmitters. Acutely, it inhibits norepinephrine reuptake, while it has no known effect on dopaminergic activity, and we know it as no known effect on serotonin activity. And that's where they reached -- in England, because that's where they reached their noradrenergic idea.

Q. Okay. What conclusions did they draw from that?

A. Well, the reading, in the abstract in here, I think the conclusion is that it -- the ability of desipramine to block reuptake contributes to its therapeutic effects.

Q. Okay. Now, there's a quote there, compared with other TCAs, DMI, et cetera, and it's talking about alpha-1, adrenergic, muscarinic, and H-1 receptors. What's that one about?

A. Well, the tricyclics, as is common with many drugs or even most drugs, their primary mechanism is described as blocking monoamine reuptake, but they also do other things in a pharmacological manner, and what they're known for is

blocking a variety of neurotransmitter receptors. And I don't know if people can see it, but again, when I say receptors, I'm talking about these postsynaptic receptors over here, and if you block those receptors, then the neurotransmitter that binds that receptor isn't sending a signal.

In the case of tricyclics, they block a variety of receptors, and that includes norepinephrine alpha-1, that includes acetylcholine, muscarinic receptors, and that includes histamine H-1 receptors as well as others.

So what this part of their paper is pointing out is that when you compare desipramine with other tricyclics, it's widely known, and we saw it in opening statements, that desipramine has lower receptor activity, weaker receptor activity than other tricyclics such as imipramine. So what they're saying is, compared to other tricyclics, desipramine is also a less potent inhibitor of these receptors. And that's viewed as a good thing in this study.

Q. Why is it good?

A. Because it 's widely taught that these receptors contribute to the side effects of the tricyclic antidepressants.

Q. What are the side effects?

A. Well, there would be a variety of them, and I'm not a clinician and I can't give you a complete list, but the

things people talk about most commonly are anticholinergic, where you block acetylcholine receptors. That can lead to dry mouth as well as many others, I believe. Sedation, which people don't know really where that comes from, but that's probably blocking alpha-1 receptors as well as other receptors. So a variety of these types of effects that are unwanted.

Q. So what conclusion do you draw from the Donnelly et al publication, Dr. Berridge?

A. That -- there are two points, I think, that are made here, is that blocking norepinephrine reuptake is effective in treating ADHD, and the fewer the receptor interaction, the fewer the receptor effects, the fewer the side effects.

Q. Okay. Let's go on to the next one, which is Trial Exhibit 25, slide 14.

What is Exhibit 25?

A. This is showing a published paper that looked at the effects of desipramine and the treatment of in this case adolescents with ADHD. This is by the group -- a group at Harvard, Massachusetts General Hospital, who are experts in child psychiatry and drug action and in treating psychiatric disorders. And they make the same --

Q. Well, before we go on there, Dr. Berridge, let me ask you a question about the group.

How well known is the group at Harvard?

A. Well, in my opinion, they're very well known. In particular, Joseph Biederman, who is currently still at Harvard in this research group, is a very prominent name in the field of ADHD and pharmacological treatment of ADHD as well as other childhood psychiatric disorders.

Q. Okay. Go ahead with your explanation of what this Exhibit 25 Gastfriend publication teaches.

A. So in this 1984 paper, they reach a similar conclusion to that by Donnelly, which is that desipramine not only -- desipramine is effective in treating ADHD, but they again point to that desipramine is a selective or more specific, as they say, in the blockade of norepinephrine reuptake relative to other tricyclics, and it -- because it has fewer receptor actions, desipramine is associated with fewer adverse effects or what I call side effects. So they're making a similar conclusion to that reached by Donnelly et al.

Q. Let's go to the next slide, slide 15, and this is Exhibit 26.

Is this the same publication that we were looking at, or is this another one?

A. No, it's the same first author, but this is in 1985, not 1984.

Q. And what does Exhibit 25 add to the picture?

A. This is again looking at the clinical efficacy of

desipramine in treating ADHD, and again, this was in adolescents, and they make similar conclusions. They point out that because desipramine has greater specificity in blocking norepinephrine reuptake, it's likely effective in treating ADHD, and because desipramine has fewer receptor actions, and they refer to this as anticholinergic and anti-alpha adrenergic effects, it's better tolerated that imipramine. It has fewer side effects.

Q. Okay. Thank you. Let's go on to Exhibit 28, slide 16.

What do we have here, Dr. Berridge?

A. This is another paper by the same Harvard group, and I believe Joseph Biederman. Dr. Biederman is a co-author on this paper. They had a large number of studies focused on desipramine in ADHD. And here, they're looking at desipramine in children, but this time it's in children with ADHD who have an additional disorder, and in this case, it's tic disorder and Tourette's syndrome.

Q. Is this consistent with or contrary to blocking norepinephrine reuptake?

A. They make -- this is desipramine, and because, as the previous studies pointed out, that desipramine is selective in its ability to block norepinephrine reuptake, it's therapeutic, but because desipramine has fewer actions at alpha-1 receptors, alpha-2 receptors, beta receptors, and

dopamine receptors, DMI is associated with less adverse effects or side effects, and they list a number of those, and they point out that this benign adverse effect, meaning lower side effect profile, has led to wide use in sensitive populations, including the elderly and children.

Q. Let's go on to the next exhibit, 129, slide 17.

What is Defendants' Trial Exhibit 129?

A. This is yet another publication from the Harvard research group. This time Dr. Biederman is the first author, and this was published in 1985. And as I said, they looked at desipramine's actions in children, and they've looked at a number of different levels of action, and in this case, they're looking at cardiovascular effects of desipramine in children and adolescents with attention deficit disorder. They point out that desipramine relatively to imipramine, another tricyclic, that desipramine is more specific in the blockade of norepinephrine reuptake, and is associated with less side effects, fewer -- reduced side effects.

Q. When somebody like Dr. Biederman talks about more specific, how does that compare with selectivity?

A. Well, the terminology that is used here is ambiguous, and I think in this case it's synonymous with selective. If it's more specific, that means it's acting in a more pharmacologically more specific way, and since what they're

talking about is reuptake, they're referring to the fact that desipramine in contrast to imipramine is not hitting serotonin reuptake, and therefore, it's more specific.

Q. How about side effects? Does Dr. Biederman talk about that?

A. Yes, down here, as I said, earlier, that they point out, as the other papers have, as all these papers have that desipramine is associated with fewer side effects. They list sedation, dry mouth, impaired cognition.

Q. Now, based on your review of the literature, some of the literature dealing with desipramine, have you formed any conclusions as to the prior art teachings of desipramine?

A. Well, I think, as outlined in all these slides, and there were other papers as well, that the conclusion to be drawn and the conclusion that these authors make is that desipramine acting as a norepinephrine reuptake blocker is effective in treating ADHD, and that because it has weaker receptor interactions, it has weaker side effects relative to the other try psych clicks.

Q. Have you prepared a slide with those conclusions?

A. I believe we did.

Q. Let's go to slide 18.

Can you go through these one by one and explain what you're talking about?

A. Well, this is just a bulleted list of what we've

discussed. Donnelly and these other papers, as we reviewed, demonstrate that desipramine is effective in treating ADHD. It's an effective drug for that disorder. It's well known, the data support the statement that desipramine is more specific or we'll get to data that say it's specific in the blockade of norepinephrine reuptake relative to other TCAs, tricyclic antidepressants, including imipramine, and that desipramine had fewer side effects compared to imipramine because it had reduced receptor interactions, including reduced anticholinergic and alpha adrenergic actions.

Q. Well, let's revisit one other point you covered earlier in your testimony.

You mentioned that you had been involved in drug discovery.

What implications do the conclusions that you have reached in slide 18 of Exhibit 553 have on how you believe a skilled worker would undertake a drug discovery effort in the field of ADHD?

A. In my experience in participating in drug discovery, the standard approach or standard model is, you look at what we know about existing drugs and you use that information to guide selection of additional drugs, compounds. And in the case of desipramine, we know it's effective, we know it blocks norepinephrine reuptake, and that's widely linked -- believed to be linked with the therapeutic effects of the

drug, and the receptor interactions of the drug are linked to side effects. So from a drug discovery perspective, then, what one would say, well, it would be nice if we had a drug that's a norepinephrine reuptake blocker and that has minimal receptor interactions.

Q. And is there such a drug out there?

A. Well, of course, there is, and the best example of that is atomoxetine.

Q. And how do you know that?

Let's go to the next slide, which is 22 -- I'm sorry, 19, and Trial Exhibit 22.

Okay. Can you tell the Court what you've got on this slide, Dr. Berridge?

A. This is a paper that compared the ability of atomoxetine, and they're referring to it as tomoxetine, highlighted down here in yellow, and a bunch, a variety of other antidepressants, including desipramine, highlighted up here. They're comparing the ability of these compounds to interact with different monoamine reuptake sides.

Q. Would you, Dr. Berridge, go through what the various columns, vertical columns represent in the Bolden-Watson paper?

A. Yes. The reason I think this paper is quite informative and relevant to the discussion is that this shows the data, this is the data, these are the data that

one would use to draw conclusions about specific actions about desipramine or atomoxetine and their ability to block different monoamine transports. And what you're seeing here are data from -- the numbers for different drugs and how strongly they interact with the reuptake site, and they are doing this for norepinephrine in this column, abbreviated NE, they're doing it for serotonin in this column, and that's abbreviated 5H-T, and they're doing it for dopamine in this column and that's abbreviated DA. And not to get into the methodology, but just to focus down that, it's a little counterintuitive when you do these types of measurements, perform these types of assays, low numbers indicate a strong interaction. High numbers indicate a weak interaction. It's an inverse type measure. And you can see that atomoxetine, which has been described as a selective norepinephrine reuptake blocker, has a low number for norepinephrine, below 1.30, and it has relatively high numbers for serotonin, we're seeing 43, and dopamine, 1,400. And really, what you have to do is look at the ratio of these, .7 versus 43, that's a big difference, and what that says is that this is selective for the norepinephrine reuptake site because it doesn't have low numbers for either of these transports. And again, that's what everybody agrees to or what is widely acknowledged.

And then you compare that with desipramine.

Desipramine has a very low number for norepinephrine and it has very high numbers for serotonin and dopamine, in fact, higher than atomoxetine.

And so if we started then with desipramine, we know it's an effective clinical drug, well, what does it do at these reuptake sites? It's very selective. Is there another compound that has a similar pattern across the different reuptake sites? And the compound that is most closely in nature to desipramine is atomoxetine. It has a low number for norepinephrine and high numbers for the other reuptake sites.

Q. Well, what about 1,400 versus 11,000; is that a significant difference?

A. In general, it isn't. What's really important is, is the ratio between this number and this number large or low if you -- depends on how you put the number in the numerator, but is it a big difference. And when you get into this magnitude difference, 40 times difference, 60 times difference, that's selective. But as I said, if anything, desipramine has higher numbers, so one would describe it as even more selective than atomoxetine.

Q. How is this data determined; do you know?

A. These data, it's a little complicated, but these data were done in rat brain, and they're using a standard measure of the strength of the interaction of the drug with these

reuptake sites.

Q. Is that an appropriate comparison, using rat brains?

A. It is for -- it is because rat brains, the monoamines of rats, their systems and their properties and the pharmacology of these symptoms is very similar to that seen in humans, and for that reason, this's why rat brains are used widely in academic research to understand how monoamines are working in humans and how you could target them and the treatment of behavioral disorders.

Q. Okay. Let's go to the next slide dealing with Trial Exhibit 24, slide 20.

Can you tell us what the Fuller-Wong paper is?

A. The Fuller and Wong paper is a paper by a group of Eli Lilly scientists who are also using rat brains to study the ability of atomoxetine and other antidepressants, in this case to interact with different neurotransmitter receptors. And we saw a very pretty slide of this in opening statement. But the point is the same, which is that when you look at atomoxetine's ability to interact with receptors, you have very high numbers, and that's indicative that it does not interact much with those receptors. So when you look across other antidepressants, atomoxetine has very low interactions with a variety of neurotransmitter receptors, and these are the same neurotransmitter receptors that were mentioned in the Donnelly and other papers that are linked to tricyclic

side effects.

Q. Okay. Thank you.

Now, considering the Bolden-Watson and Richelson and Fuller and Wong papers together, what conclusions do you think a person of ordinary skill in the art would reach based on this literature?

A. Well, I think what those two papers show is that desipramine and atomoxetine, Bowden-Watson and Richelson show that atomoxetine is similar to desipramine in its ability to selectively block norepinephrine relative to the other monoamine transporters that are commonly targeted by tricyclics.

And then Fuller and Wong is teaching us that atomoxetine has fewer receptors, interactions with receptors, and we know that that has been linked to side effects associated with tricyclic antidepressants, including desipramine.

Q. Okay. Let's look at the last Graham factor, if you pull up slide 23.

Now, the last slide are different from the prior art and the claims. Have you reached an opinion as to what, if any, differences exist between the prior art you've discussed and the claim of '590 patent ?

A. Well, I see very little difference between the prior art and the claim. The prior art is teaching norepinephrine

reuptake blockers are effective, and really, the only difference is that the patent or the claim explicitly mentions the use of atomoxetine in treating ADHD.

Q. Okay. Now I'd like you to take another step further. I want you to consider Donnelly in combination with Bolden-Watson and Richelson and Fuller and Wong. What conclusions do you believe a person of ordinary skill in the art as you've defined it would reach based on considering those three prior art publications?

A. I hate to be repetitive, but I think that what those clearly indicate is that selective norepinephrine reuptake blockers, including desipramine, are effective in treating ADHD. The side effects of tricyclic antidepressants, including desipramine, are linked to receptor interactions, and that atomoxetine being a selective norepinephrine reuptake blocker with minimal receptor activity would be an obvious candidate for treating ADHD.

Q. Thank you.

Now, let's go to a slightly different topic.

Now, you've already mentioned you didn't find any data in the patent that told you that atomoxetine would be effective in treating ADHD.

What do you believe a person of ordinary skill in the art would derive from the teachings of the patent?

A. Can you repeat that question?

Q. Sure.

What do you believe one skilled in the art would understand from the rationale that was provided in the '590 patent as to the basis for the statement that atomoxetine would be effective in treating ADHD?

A. The only rationale I can see is the literature, the prior art that I've pointed out, that desipramine being a selective norepinephrine reuptake blocker is effective in treating ADHD because, as I said, there was no data in the patent indicating that atomoxetine would have efficacy in the disorder.

Q. If you're wrong in that view, if the prior art doesn't suggest atomoxetine, what conclusion do you reach as to the rationale for the disclosure of utility in the patent?

A. You're going to have to repeat that one.

THE COURT: Yes, I'd have to hear that question again, too.

MR. ROCKEY: Okay.

THE COURT: Want it read back?

MR. ROCKEY: Sure. Why don't we read it back?

(Record read)

A. Well, I'm not sure what "disclosure of utility" means.

Q. Let me withdraw the question and rephrase it.

If you're incorrect in the view that you express, is there any rationale contained in the patent that would

explain the basis on which atomoxetine would be used in the treatment of ADHD?

A. No, there's no rationale provided for using atomoxetine in the absence of prior art. So the prior art is irrelevant. I see no rationale for using atomoxetine.

Q. Okay. Have you looked at any other evidence in this case that have affected your views on that?

A. On that last point?

Q. Yes, on that last point.

A. Well, there's the testimony by one of the inventors, Dr. Heiligenstein, which we've heard reference to earlier.

Q. Okay. Well, let's pull that up.

Did you understand Dr. Heiligenstein to be saying that he didn't know whether his invention would work?

A. It is what I understood, and here's an excerpt from the testimony which is very similar to what we heard:

Did you have a reasonable expectation that it would work? And he answered, "It was a hypothesis. The hypothesis would not have been generated by the fact that it was a selective norepinephrine reuptake inhibitor."

Can we go to next slide?

Q. We were just talking about slide 25. Let's go to slide 26.

A. Okay.

Q. This is more Heiligenstein testimony, isn't it?

A. It is, and here, he just makes the point that I've stated, that he says, well, there is no scientific data that supports that, which is referring to this statement up here, the statement in the patent that tomoxetine is effective in treating ADHD, and he says there's no scientific data from tomoxetine studies.

Q. Okay. Let's go on to the next slide, 27.

A. And then, again, he just says, when he was asked, did you believe -- reasonably believe it was going to work, he says, I had no idea if it would work, no idea.

MR. ROCKEY: Your Honor, I think I'm just about done, if I can take a minute.

THE COURT: Certainly.

MR. ROCKEY: I have no further questions, Your Honor.

(Off the record discussion)

MR. ROCKEY: I just want to clarify, there are no objections to the demonstratives I've offered from Exhibit 553, Your Honor.

MR. LIPSEY: No objection as demonstratives, Your Honor.

THE COURT: Okay. Wait. I don't know what that means.

MR. LIPSEY: I mean, I assume they were demonstrative evidence.

THE COURT: Well, if they're demonstrative, there's nothing else we have to do with them. If they're being offered in evidence, there's something we have to do with them.

MR. ROCKEY: That's what I'm doing, Your Honor.

THE COURT: You're offering them into evidence.

MR. ROCKEY: Into evidence.

THE COURT: Any objection?

MR. LIPSEY: May I reserve on that? Perhaps we can work out a stipulation that either they all come in or they all don't, and I think we can try to work it out.

THE COURT: Okay.

MR. ROCKEY: Fine, Your Honor.

THE COURT: Now, do you want to start, or do you want to break for lunch? What do you want to do?

MR. LIPSEY: I think it might make sense to break for lunch. We have a fairly large volume of documents that we have to get out.

THE COURT: Okay. I thought we'd take seven or eight minutes for lunch.

(Laughter)

MR. LIPSEY: Your Honor, I can be ready in five.

THE COURT: How long do you want to break for lunch? Forty-five minutes, an hour?

MR. LIPSEY: I think an hour.

THE COURT: An hour? Everybody.

Okay. By the way, that clock is wrong. It's somewhat slow. The Federal Government has paid, I don't know, three, $400,000 trying to fix that clock. We can't do it. So it's about 12 o'clock, so we'll come back here at one.

MR. LIPSEY: Okay. Thank you.

THE COURT: Okay. Doctor, you may step down.

THE WITNESS: Thank you.

MR. ROCKEY: Thank you, Your Honor.

THE COURT: One o'clock.

(Luncheon recess taken)

A F T E R N O O N S E S S I O N

THE COURT: Be seated.

Okay. Everyone's back.

Ready to start cross-examination?

MR. ROCKEY: Your Honor, before Mr. Lipsey begins, I just want to make sure the record is clear. We talked about the exhibits, and there is no objection to the ones contained in Exhibit 553 --

THE COURT: Is that so?

MR. ROCKEY: I'm not quite done.

-- Trial Exhibits 1, 22, 23, 24, 25, 26, 28, 47, and 129.

MR. LIPSEY: Those are Defendants' Trial Exhibits, and there's no objection to them.

THE COURT: Okay. They will be in evidence. What wasn't?

MR. ROCKEY: Well, what he is doing is reserving his objection on the demonstratives.

MR. LIPSEY: We're trying to work out some kind of mutual arrangement on them.

THE COURT: Okay.

MR. ROCKEY: So we'll see if we can get that done.

THE COURT: Those are in evidence. The others, we'll reserve.

MR. ROCKEY: Thank you, Your Honor.

THE COURT: Okay. Let's proceed.

(Defendants' Trial Exhibits 1, 22, 23, 24, 25, 26, 28, 47 and 129 marked in evidence)

MR. LIPSEY: Thank you, Your Honor.

CROSS-EXAMINATION

BY MR. LIPSEY:

Q. Good afternoon, Dr. Berridge.

A. Good afternoon.

Q. My name is Charles Lipsey. I represent Lilly. I did not have the pleasure of being at your deposition, but I've had the pleasure of reading your handiwork.

Have you fully expressed the opinions on the obviousness and enablement utility issues in this case?

A. I have fully expressed my opinions on the obvious issue. I haven't expressed opinions on the second category.

Q. But you're not consciously holding something back?

A. I'm sorry, can you repeat that?

Q. You're not consciously holding something back on the obviousness issue, are you?

A. No.

Q. You haven't -- the reason I ask is that there were 30 references in your expert report, and now there are seven that you've relied upon, and I just want to make sure that those are the seven that we're going to be focused on. Is

that your understanding?
A. No, I don't have an understanding related to that. I'm happy to talk about everything that was in my expert witness report.
Q. But you didn't hold back any of your opinions in your direct testimony; correct?
A. No. No. The sampling I -- we focused on today represents the most important parts that I consider the most important parts of my report.
Q. Now, and of those seven references that you're now relying on, five of those were published before you got your Ph.D. in 1988; correct?
A. If that's -- that sounds about right, yes.
Q. Let's chat a little bit about your CV, Defendant's Trial Exhibit 47.

Can you identify for me which publications on your CV relate to new human drugs that you have developed?
A. I have not developed new human drugs. I worked with compounds that were identified as drug -- by drug discovery programs that they felt might have potential at some point in human use.
Q. Okay. But you have not --
A. And that's the nature of the drug discovery program.
Q. But you yourself have not developed new drugs for human use; correct?

A. No.

Can I just add, I haven't worked in drug development, so that's why. That follows.

Q. Now, the bulk of your work related to ADHD has actually been directed to the study of the stimulants; is that right?

A. Correct.

Q. Can you identify for me which of the publications on your CV relate to ADHD work you did with desipramine?

A. I have not done work with desipramine.

Q. Can you identify for me which publications on your CV relate to ADHD-related work you did with a tricyclic depressant?

A. There would be none.

Q. I'm sorry, antidepressant.

A. There would be none.

Q. Now, the only publication on your CV prior to January of 1995 that refers to ADHD is this publication number seven, your 1993 paper in "Physiological Medicine"; is that correct?

A. That's correct. Didn't start working on the pharmacology of ADHD until the early -- around 2000.

Q. Okay. And the reference in that 1993 article is simply to cite Dr. Hunt's 1985 article about the use of clonidine in ADHD; correct?

A. No, I don't think that's entirely accurate. In that 1983 article, we're talking about the degree to which postsynaptic alpha-2 receptors in the prefrontal cor text promote cognitive function, and -- just basically, and then we make the extension that that action would be useful in treating disorders associated with impaired cognition, and then we make an extension of that to ADHD.

MR. LIPSEY: Objection; nonresponsive. Move to strike the answer.

THE COURT: Well, wait. Wait. Wait. How would I possibly know if it's not responsive? I've got a heading.

MR. LIPSEY: Okay. Point well taken, Your Honor. May I approach the witness?

THE COURT: Sure.

MR. LIPSEY: As a matter of style, should we ask, or should we assume --

THE COURT: You can feel free to float around.

(Laughter)

Q. I'm handing you a copy of that 1993 article, marked for identification as Defendant's Trial Exhibit 68.

A. Yes, sir.

Q. And that is the article that is referenced, it's reference number seven on your CV; correct?

A. Can I just -- do you want me to make sure of that?

THE COURT: Sure.

A. Correct.
Q. And if you turn to page 561, under "Clinical Implications" --
A. Correct. Yes.
Q. And halfway down the second paragraph, the statement is made "and attention deficit disorder (attention regulation and impulsiveness) (Hunt et al 1985)." Do you see where I've read?
A. That is correct.
Q. And that's the only reference to attention deficit disorder in this paper; correct?
A. Well, I'm not -- that is correct. I'm not sure I understood your question.
Q. That's fine. That's all I was asking.
Now, the only publication -- the first publication that I saw on your CV that actually mentioned ADHD in the title is this 2001 article, reference number nine on Defendant's Trial Exhibit 47; is that right?
A. That's correct. And that's about when I became interested in the pharmacology, interested in studying the pharmacology of ADHD. And it was because of my participation in that book that I became interested in the pharmacology of ADHD.
Q. Okay. And your chapter in that book was in the section on basic neuroscience; right?

A. Correct.
Q. And one of the things that caught your eye at that time relating to your perceived importance of norepinephrine was an observation that low doses of the stimulant methylphenidate actually affected norepinephrine, but not dopamine; correct?
A. No, I don't think that's accurate. What I think isn't accurate is the, not affecting dopamine. I think it affects dopamine. I think it has stronger action on norepinephrine. But I'm not sure that's confined to low doses. I think that's a general property of methylphenidate.
Q. I'll hand you a copy of that article appearing in "Stimulant Drugs and ADHD."
A. Thank you.
Q. That is the book chapter listed on your CV; correct?
A. It is listed in my CV.
I think I do know the issue you're talking about.
THE COURT: Well, wait. Listen to the question.
THE WITNESS: Okay.
Q. And if you turn, please, to page 172.
A. Yes.
Q. The last few sentences before the heading there --
A. Yes.
Q. -- it says: "Of potential greater significance to the current discussion, recent observations by Kuczenski and

Segal (personal communication) indicate that at low doses (.5 milligrams per kilogram sc) methylphenidate elicits significant increases in NE efflux in the absence of changes in extracellular dopamine levels as measured by in vivo microdialysis."

That is what you wrote then?

A. That is what the preliminary observations suggested, yes.

Q. And that was an observation that led you to believe that norepinephrine might be particularly important in ADHD; correct?

A. No. Not accurate. No. And can I explain, or do you want to follow up?

Q. Well, you make the same comment at the top of page 174; correct? The first complete sentence: "Finally, the preliminary observations described above of a selective increase in NE efflux and not dopamine at lower doses of methylphenidate further strengthens the hypothesis that therapeutic actions of amphetamine-like stimulants in the treatment of ADHD involves alterations in NE neurotransmission."

That's what you wrote then.

A. That's what it says. The involves, though, does not say that --

Q. That's -- that's what you said?

MR. ROCKEY: Your Honor, may he explain his answer?

THE COURT: You know, if I had a jury here, I think I would say, counsel, you can straight this out on redirect. But there's no jury here. It's evident that this witness wants to make an explanation as to his comment. I think it's appropriate that I hear it.

THE WITNESS: Thank you, Your Honor.

MR. LIPSEY: Fair enough. Fair enough.

THE COURT: All right.

A. All right. So this says -- let me -- the word "involves" does not mean solely due to norepinephrine. It just means it involves. The literature at that point when I wrote this article, which was not 1995, put an emphasis on the involvement of dopamine in the therapeutic effects of psychostimulants at the exclusion of norepinephrine. This was highlighting the fact that one shouldn't ignore the possibility role of norepinephrine in the therapeutic effects. And although the work by Kuczenski suggested, well, maybe low-dose methylphenidate has a stronger action on norepinephrine, my next -- where I took this paper in my next chapter or my next paper related to ADHD focused on a different part of the brain, where we had reason to think that low-dose methylphenidate might target both norepinephrine and dopamine. And I've never once suggested

that psychostimulants are therapeutic through only their actions of norepinephrine. In fact, I've suggested that both transmitters are important.

Q. Okay. And the observation we're talking about was a recent observation in 2001; correct?

A. The observation that I just ended up on is 2006. But when I was writing this, that's the direction we were going, and the reason I chose a different region than the Kuczenski observations is because I had reason to think the drug would do something different in that region. And I've never once thought norepinephrine was the sole story behind psychostimulants.

Q. Now, while you were writing this book chapter on "Basic Neuroscience," the chapter in the section on "Clinical Neuroscience" relating to "Comparing the Effects of Stimulant and Non-Stimulant Agents on Catecholamine Functions: Implications For Theories of ADHD" was being written by Dr. Pliszka, correct?

A. Okay.

Q. And you read Dr. Pliszka's chapter at the time that you were writing your chapter; correct?

A. I don't know if I read it. It certainly was distributed among the participants in the book, and we attended a meeting where everyone shared their information.

Q. And you cited Dr. Pliszka's chapter 14 on page 159 of

your chapter; correct?
A. Which page?
Q. 159, at the top, halfway down, the first paragraph.
Let's get chapter 14.
A. Yes.
Q. And you knew from Dr. Pliszka's chapter that tomoxetine had been used to treat ADHD in 2001; correct?
A. You know, I can't give a definitive answer to that. I don't remember what I knew about Dr. Pliszka's chapter when I made this -- when I cited this. It's possible that the editor suggested I cite this at this point, though it's possible I did it on my own. I really -- at this point, I can't tell you.
Q. Let's try to cut through it, then.
You were aware that tomoxetine had been shown to be safe and effective for the treatment of ADHD before you were retained as an expert in this case; correct?
A. I had known that atomoxetine was used in the treatment of ADHD, and it's probably right around here that I had heard about it.
Q. And that's something you knew about before you ever sat down to do your obviousness analysis; correct?
A. Yes. Yes.
Q. And you mentioned double-blind studies as being the most reliable indicator. Why is that?

A. Because they avoid any potential bias from the investigator that might push the data in a particular desired direction.

Q. Because if the investigator knows what it is he's looking for, he might see it even if it's not there; correct?

A. Right.

Q. Now, you are not a medical doctor; correct?

A. Correct.

Q. And you've never treated a patient with ADHD; correct?

A. Correct.

Q. You've never tried to diagnose a patient with ADHD; correct?

A. Correct.

Q. And you've never tried to determine whether medication given to a particular patient for ADHD improved the symptoms of that patient; correct?

A. Correct.

Q. And you're not a clinical pharmacologist; correct?

A. Correct.

Q. And I think you said you didn't focus on ADHD in your research until around 2000; is that right?

A. Correct.

Q. And you didn't do any research or other work related to ADHD prior to that time; correct?

A. Correct.
Q. Now, the question of why clinical doctors use a particular medication to treat ADHD is outside of your area of expertise; correct?
A. That is correct.
Q. I apologize if I've already asked this. Are there any publications on your CV that cite any of the references to desipramine that you rely on prior to 1995?
A. No, I don't think so.
Q. Are there any on there that cite any of these desipramine references you rely upon even today?
A. I don't think so.
Was the "today" in reference to what I cited today, or any articles that I've written that cite?
Q. I was referring to whether you had referred to it in any of your articles, even today.
A. Today, I have. They're probably not on your CV because that's a year old.
Q. Now, you have several volumes in front of you. I probably should have done this first. Volume 1 is your expert report and its attachments --
A. Okay.
Q. -- in case you want to look at it. Volume 2 is your deposition transcript in case you want to look at it. Volume 3 is the patent-in-suit, its file history and the

tandamine reference. Volume 4 is the prosecution history of U. S. Patent 5,441,985, Defendant's Trial Exhibit 122, which you had also reviewed in your report. And Volume 5 is a collection of references.

A. Okay.

Q. Okay. In Volume 5, if you could please turn to tab 17, Defendant's Trial Exhibit 23, that's the Donnelly reference that you rely upon in support of your opinion here; right?

A. Correct.

Q. Can you turn, please, to page 78? And over in the right-hand column, the last complete paragraph, starting "The literature...." Donnelly and others report here: "The literature describing the neurochemistry of learning and memory is voluminous, complex, and often contradictory. Noradrenergic, dopaminergic, cholinergic, serotonergic, peptide, and neurohormonal systems - both central and peripheral - have been implicated in various cognitive processes. It has been suggested that dopaminergic and cholinergic mechanisms may be more important than noradrenergic mechanisms for information processing tasks that require attention-demanding or effortful cognitive activity."

Do you see where I've read?

A. I do.

Q. Okay. And you don't disagree with that; correct?
A. I don't disagree with that.
Q. And you would agree that as of January 1995, the cause and mechanism of ADHD were not known; correct?
A. Correct.
Q. And you would also agree that even today, the causes and mechanisms of ADHD are not known.
A. Correct.
Q. And that's despite studies since the 1930's concerning ADHD; correct?
A. That is correct, yes.
Q. And even as of today, not much is understood about the biology of ADHD; correct?
A. That is certainly true.
Q. And the neurotransmitter bases for ADHD is not understood even as of today; correct?
A. Correct.
Q. The scientific data do not strongly implicate the prominent involvement of a single transmitter in ADHD; correct?
A. Yes, that's related to the last point you made.
Q. And that's because the brain is a complicated thing, with hundreds of transmitters, lots of different regions, and lots of different cell types; correct?
A. Correct.

Q. Sounds familiar; right?

(Laughter)

A. It's an understatement.

Q. And as of January 1995, there was no way to see into the human brain to see what the drugs were doing that might affect the norepinephrine transmission system; correct?

A. In the human, that's correct.

Q. And I've seen in your publications you've done a lot of work with the portion of the brain called the locus coeruleus. Did I pronounce that right?

A. You did.

Q. Okay.

A. And I have.

Q. And may we agree that we'll call that the LC, just to save everybody the trouble?

A. Sounds good to me.

Q. Okay. And you're aware that as of January 1995, there were theories concerning whether the norepinephrine neurons in the LC were firing too much or firing too little in ADHD; correct?

A. There were theories.

Q. And there was no consensus at that time as to whether in ADHD the norepinephrine neurons in the LC were firing too much or too little; correct?

A. That's correct, because we don't understand then or

now the neurobiology of ADHD.

Q. And it's fair to say that there is no widely accepted monkey model of ADHD; correct?

A. There is no widely accepted animal model of ADHD, including monkeys.

Q. And that would include the aged monkey; correct?

A. Correct.

Q. And that's because the aged monkey doesn't share the features of ADHD; correct?

A. Correct, in many respects.

Q. And animal models of attention are not necessarily models of ADHD; correct?

A. No. There is no good animal model of ADHD.

Q. And that's because there are multiple forms of attention, and the attention effects that have been studied in animals and human subjects are not necessarily the same types of attentional mechanisms that are affected in ADHD; correct?

A. That is part of the answer, yes.

Q. Now, at the risk of beating a dead horse, I gather you would concede that the belief is that there's a role for dopamine as well as norepinephrine in the pathology of ADHD; correct?

A. I think that -- in the pathology of ADHD? No, I don't agree with that.

Q. Well, let me rephrase that.

You would agree that in addition to norepinephrine, there was a role for dopamine as a potential contributor to the pharmacology of ADHD.

A. I would agree to that. I do agree to that.

Q. And, indeed, if you take a look at Donnelly, Defendant's Trial Exhibit 23, tab 17 that we were just in, and you look at page 79, top of the right-hand column, the first complete sentence, that was known back in 1986 also, that dopamine and norepinephrine were likely involved; correct?

A. Yes, that comes from a comparison of stimulant action versus compounds like desipramine.

Q. Now, in Donnelly, Trial Exhibit 23, if you turn to page 79 again, and over in the left-hand column, the bottom paragraph, that's a discussion of the apparent relationship of norepinephrine to the treatment of ADHD; correct?

A. Correct.

Q. And the point that Donnelly and others make here, down about the middle of the paragraph, is that the relationship is not simple; correct?

A. Give me a second. Let me read it.

Q. Sure .

A. That statement is taken in a context of a discussion of MHPG and other indirect -- my guess is other measures of

norepinephrine and other neurotransmitter action, and that is the statement -- that statement's coming from a discussion of this relatively indirect measure called MHPG.

Q. But at the time of Donnelly, they do state that the relationship between norepinephrine and the treatment of ADHD is not simple; correct?

A. They say that, based on these MHPG data, and I think that's a significant point.

Q. Okay. And the first reason they give in the next clause is because DMI, which is desipramine, "has been shown to affect other neurotransmitters centrally "; correct?

A. Correct.

Q. And at the bottom --

A. But the citation to that statement is a review article that I think would contradict the data table I presented earlier.

Q. I'm sorry?

A. They cite number 14, a paper. It's a review article, I think, and they're not looking directly at the degree to which DMI is specifically interacting with different transporters. So I'm not sure that that -- you know, that statement is there, and they cite reference 14 as evidence for it, but I'm not sure I would agree with their statement there.

Q. They make the statement.

A. They make the statement.
Q. And the paper that they cite is Dr. Potter's paper of the NIMH where he showed that desipramine also could affect serotonin; correct?
A. They show that desipramine can affect serotonin metabolites, which are an indirect way of measuring whether it affects serotonin. So I don't think that's a definitive observation.
Q. Okay. That's a view that you formed sometime in 2000, looking back at these papers?
A. No, that's a view I was taught in my first year in graduate school in 1984, that these measures that they're focusing on are indirect measures, and although they are often related to release in neurotransmission, they can be influenced by other mechanisms. And this is something I teach today to my undergraduate and graduate students.
Q. The first time you reviewed this Donnelly reference was sometime after 2000; correct?
A. That's correct.
Q. And there's a reference in the same paragraph to mianserin down there towards the bottom. Do you see that?
A. I do.
Q. The statement is made: "...and mianserin, which presumably produces similar alterations in noradrenergic metabolism (plasma NE levels were increased by 36 percent in

the small group studied), was not clinically effective in the treatment of ADHD ADDH." Do you see where I've read?

A. Yes.

Q. And mianserin was a drug that was thought at this time to increase norepinephrine levels in the synapse; correct?

A. The answer in one of its actions is to block norepinephrine reuptake. What's relevant to this discussion and relevant to what I said earlier, it also blocks these alpha-2 receptors, which is what another class of drugs that are used to treat ADHD stimulate. So one might draw the conclusion that when you have a few norepinephrine reuptake blockers that are effective in ADHD, desipramine, nortriptyline are the primary examples, and a third doesn't have the same behavioral effect, but it has a different neurochemical reaction, I think the person of ordinary skill in the art would say, well, maybe that's the reason why he didn't like the others.

Q. That's not what Donnelly said here; right?

A. No, it's not what Donnelly says here.

Q. And I think you noted that the authors of this publication include not just Donnelly, but they include Dr. Zametkin, Dr. Rapoport, and Dr. Potter; correct?

A. Correct.

Q. All of the National Institutes of Mental Health; correct?

A. Correct.
Q. And that was a meeting group in the ADHD field in the 80's and early 90's; correct?
A. Correct.
Q. And while we're in the book, if you can turn, please, to tab 12, Plaintiff's Trial Exhibit 621.
A. I'm sorry, which book are we looking at?
Q. The book that's got the reference in it.
THE COURT: The same one.
A. Volume 5. Thank you.
Q. It's Plaintiff's Trial Exhibit 621. That's the Langer article describing the failure of mianserin in ADHD.
A. So we're in volume 25 at reference 21?
Q. I'm sorry?
A. Volume 25 at --
Q. Tab 12.
A. Twelve. I'm sorry.
Okay.
Q. That's the Langer publication describing the failure of mianserin in the ADHD trial; right?
A. Okay. Correct.
Q. And if you turn to tab 15, Plaintiff's Trial Exhibit 314, that's the Hunt 1985 article that you cited in your 1993 paper; correct?
A. Correct .

Q. And it's discussing clonidine; right?
A. Yes.
Q. If you turn to page 618, under the heading "Clonidine," they report there that "Clonidine is an alpha-adrenergic stimulating agent which acts preferentially on presynaptic alpha-2 neurons to inhibit noradrenergic activity." I'm skipping the citations. It states: "It stimulates release of growth hormone and inhibits norepinephrine release...." Do you see where I've read?
A. Yes.
Q. And that is how Hunt characterized clonidine in 1985; correct?
A. In 1985, before post --
Q. Clonidine was nonetheless thought to be at least partly effective in treating ADHD at that time; right?
A. At that time. In 1985, postsynaptic alpha-2 receptors weren't widely recognized to exist, so everyone did focus on the presynaptic alpha-2 receptors in 1985. That changed later, a few years later, and by the early 1990's, there was substantial evidence to suggest postsynaptic alpha-2 receptors exist and they promote cognitive functions similar to that seen in ADHD.
Q. While we're at it, if you turn to tab 16, Defendant's Trial Exhibit 59, that's Dr. Hunt's paper in 1986; correct?
A. Correct.

Q. If you turn to page 230, upper left-hand side, it's got the same statement in there, that clonidine inhibits norepinephrine activity; correct?

A. Yes, and before the discovery of postsynaptic alpha-2 receptors, clonidine's ability to treat ADHD was confusing.

Q. I'd like to hand you a copy of a publication by Wayne H. Green, M.D., Plaintiff's Trial Exhibit 614.

You recognize Dr. Wayne H. Green as a reliable authority in the field of ADHD; correct?

A. I recognize that he wrote a chapter on the pharmacological treatment of ADHD.

Q. And you cited the 1992 chapter that he wrote on the same topic in your expert report; correct?

A. I did.

Q. Okay. So you regard Dr. Green as a reliable authority on this topic; correct?

A. I don't know much about Dr. Green and his qualifications. He has written the chapter I cited, and I found it a useful source, but not necessarily a definitive source. But when you --

Q. Not necessarily what?

A. Not necessarily a definitive source.

Q. That wasn't my question. My question is, he's a scientist --

A. I don't know much about Dr. Green, and I don't have an

opinion on his qualifications or his degree of authoritativeness in this topic.

Q. You found his writings on this topic sufficiently reliable to cite them in your own writings.

A. Yes.

Q. And if you would turn, please, to page 186, under the heading "Alpha Adrenergic Antagonists," Dr. Green writes there: "Clonidine, a centrally acting antihypertensive agent, is an alpha-2 noradrenergic receptor agonist that acts preferentially on presynaptic neurons to inhibit endogenous release of norepinephrine in the brain."

That's what he wrote.

A. That's what he wrote.

Q. And this publication is dated in January of 1995.

A. Right. And partially accurate, but as I said, he's ignoring the fact that there are postsynaptic alpha-2 receptors. He clearly didn't keep up with the literature on this aspect. But you know, he's speculating on how the drug works. But he's ignoring relevant information in that speculation.

Q. He was working in the field in January 1995 and you were not; correct?

A. My impression is he has clinical expertise.

Q. Now, as of January 1995, serotonin could not be definitively ruled out as a potential contributor to the

pharmacology of ADHD; isn't that right?
A. As of 1995?
Q. Yes.
A. I think the weight of the information would suggest it wasn't effective, and I think that's stated by some of the people we've reviewed. I do understand that there were limited publications that suggest maybe it was. But across the ones I looked at, the majority stated serotonin reuptake blockers were ineffective in the treatment of ADHD.
Q. But you agree that serotonin could not be definitively ruled out as a potential contributor to the pharmacology of ADHD in January of 1995; correct?
A. I don't know about that. I think the citations that we've cited and that Dr. Pliszka cited state that SSRIs are ineffective in the treatment of ADHD.

Now, I do know there are others out there, but I think that these definitive statements, and I didn't go and look at the quality of the studies, but it seemed to me that there was consensus on this, even if it wasn't unanimous.

Q. You have your deposition up there in Volume 2?
A. I'm sure I do.
Q. On page 78, starting at line 15, you were asked:

"QUESTION: Anything else?

"ANSWER: Those are the most commonly discussed. There were, depending on who you read, discussions of

serotonin, but drugs that block reuptake of serotonin, there were mixed results with those drugs in clinical trials, and so many people, most people, including Dr. Pliszka, I believe, concluded that serotonin probably wasn't the most relevant transmitter to be focusing on.

"As we talked about, Mefford and Potter talked about epinephrine, but as we talked about, I don't see that as being supported in the literature as the most obvious one to start talking about, though it could participate."

Correct?

A. In the context of epinephrine, that's correct.

Q. Let's take a look at the Zametkin publication. And that should be tab 18, Defendant's Trial Exhibit 33.

THE COURT: Are you back to Volume 5?

MR. LIPSEY: I'm sorry?

THE COURT: Five?

MR. LIPSEY: Five.

THE WITNESS: And which number in there?

Q. Tab 18, Defendant's Trial Exhibit 33.

A. Yes.

Q. This is a 1987 review article written by Drs. Zametkin and Rapoport; correct?

A. Correct.

Q. They were some of the co-authors on the Donnelly paper; correct?

A. Correct.
Q. And this was a review article; correct?
A. Yes.
Q. Now, you didn't read this article when it came out in 1987, did you?
A. No, I didn't.
Q. And this review article attempts to summarize 50 years of studying ADHD in medications; correct?
A. They were ambitious, and yes.
Q. Okay. Would you turn to page 678, please?
Over there on the right-hand side, in the second-to-last complete paragraph, starting "The more recent reports," --
A. Yes.
Q. -- there is reference there to arguing for a pathological hyperfunctioning of the noradrenergic system in ADHD. Do you see that?
A. Yes. Yes.
Q. And that is a suggestion that there's too much norepinephrine in ADHD; correct?
A. They are speculating about the biology of ADHD, and they are speculating there is too much norepinephrine, correct.
Q. Okay. And right below that, there's some discussion of some animal studies that suggest that norepinephrine

depletion provides an animal model for attentional deficits. Do you see that?

A. Yes.

Q. So that's a suggestion that there may be too little norepinephrine in ADHD; correct?

A. From that animal model, yes.

Q. In the first sentence of the next paragraph, Drs. Zametkin and Rapoport state: "Support for a noradrenergic hypothesis (leaving aside the issue of over or underactivity) comes from several areas."

Do you see that?

A. Yes.

Q. And that indicates that these authors are not taking a position as to whether there's too much or too little norepinephrine in ADHD; correct?

A. Yes.

Q. You would agree that --

A. Well, sorry. Can you repeat your question?

Q. That indicates that these authors are not taking a position as to whether it's too much or too little norepinephrine in ADHD; correct?

A. No, it sounds like they're saying there is a support for a noradrenergic hypothesis, but they're not saying that there's too much or too little, but they're hypothesizing there's a norepinephrine involvement in the disorder.

Q. But they are not taking a position as to whether it's too much or too little; correct?

A. That's -- yes, I agree.

Q. And you agree that the noradrenergic hypothesis refers to the theory that ADHD involves a disregulation of norepinephrine in some form; correct?

A. Yes, in this paragraph, I think that's what it's referring to.

Q. And you agree it was called a hypothesis because it was not proven; correct?

A. It was not proven, but there were observations that led one to that hypothesis.

Q. And it's still not proven even today; correct?

A. Correct. We do not understand the neurobiology of ADHD.

Q. And if we move on to page 679 in Defendant's Trial Exhibit 33, the Zametkin and Rapoport paper, and you look at the sentence bridging the columns at the bottom of the page, they go on to state: "Thus, change in noradrenergic function might be necessary, but it is not a sufficient condition for improvement in ADDH."

That was their conclusion; correct?

A. That was their conclusion in this paper. It's based on an observation with MHPG. You can see it in the other paragraph just before you start highlighting. As I said,

that is an indirect measure. It is fraught with limitations. People who use it as an index of norepinephrine transmission need to treat it carefully, and when you compare that one observation against the bulk of the known pharmacology where it's factual, not assumption, that statement doesn't make much sense.

Q. Just so that hopefully the Judge is with us at least at some point, MHPG refers to a metabolite of norepinephrine; right?

A. Yes. The more -- after norepinephrine is released, it gets taken up, monamine oxidase acts on it, converts it to MHPG, and under many conditions, the more norepinephrine you have released, the more you get taken up, the more you have broken down, so MHPG is an indirect measure of that. But many things influence -- can influence that concentration.

Q. That metabolite can show up in the blood or in the urine; correct?

A. It can.

Q. And --

A. And there, it's primarily measuring peripheral transmitters.

Q. But there was no way to get into the human brain and actually measure what was going on in a live patient; correct?

A. There was no way to get into the human brain. There

were many animal studies where you could measure norepinephrine directly, and those -- levels directly and not the breakdown product in indirect, and those studies give rise to what is a widely held belief that these drugs work to increase levels of norepinephrine, desipramine and like compounds, and that the whole foundation of biomedical research is on the assumption that the way it's working in the rat is the same way it's working in the human in general terms.

Q. The question I asked was, there's no way to directly measure it in a human brain, and the answer to that question is yes?

A. That's correct.

Q. Okay. Thank you.

And clinicians are interested in long-term measures in the human of the effect of these drugs on the noradrenergic system; correct?

A. Clinicians who are treating patients, yes. Clinicians who might participate in drug discovery, no.

Q. But clinicians who are interested in the long-term effects, that's the only tool they had back then; isn't that correct?

A. That's the only tool. That's why we use animals, to further our understanding of how these drugs are working in humans.

Q. The MHPG measures that Zametkin and Rapoport are referring to are the only measures available to clinicians to gauge the long-term effects on the norepinephrine system; correct?

A. That's correct. But it's not a strong observation.

Q. Thank you.

Okay. And then returning to Zametkin and Rapoport, Defendant's Trial Exhibit 33, if you turn to their summary --

THE COURT: Wait. What's the number?

MR. LIPSEY: It's still at tab 18.

THE COURT: I've got it. Go ahead.

Q. And it's at page 684, under "Summary," the second paragraph, the single sentence, two-sentence paragraph, they state again as their summary: "Alteration in noradrenergic function appears necessary but not sufficient for clinical efficacy." That was in their summary; correct?

A. That was in this chapter summary. It was not in another paper they published in the same year where they talk about norepinephrine mechanisms in treatment.

Q. That is in the chapter summary of this a review article summarizing 50 years of work.

Now, if you turn back to 680, looking in the right-hand column, there's an italicized heading there that states: "Single neurotransmitter hypothesis: Untenable."

Correct?

A. Correct.

Q. And you interpret that heading to mean that the pathophysiology of ADHD is not based on a single transmitter; correct?

A. I would have to read the paragraph. That certainly could well be true. It could also be talking about how you get optimal therapeutic benefit from drugs to treat ADHD.

Q. The statement they make in this article in 1987 is that the single neurotransmitter hypothesis is untenable; correct?

A. That's what they're saying. You asked me -- this is in reference to the biology of ADHD, and I didn't read the paragraph, so I'm not sure what it's in reference to.

Q. And you agree that the scientific data do not strongly implicate a prominent involvement of a single neurotransmitter in ADHD; correct?

A. In the pathology of ADHD?

Q. Yes.

A. Yes.

Q. And while we're in Zametkin and Rapoport, if you could turn to page 682, we see in the left-hand column there a heading "Future Directions." Correct?

A. Yes.

Q. And the first topic discussed there are

pharmacological studies; correct?
A. Yes.
Q. And if we go over to the top of the right-hand column, the last sentence there is one where they propose trials of a combination of dopaminergic and noradrenergic agents. Do you see that?
A. Yes.
Q. And that's not tomoxetine; correct?
A. That's not tomoxetine. This is a comment in reference to how do you mimic the optimal therapeutic effects of psychostimulants, which are undisputed to be more effective than desipramine, and the data would certainly argue that to get the same efficacy of the stimulants, one would want to increase dopamine and norepinephrine simultaneously.
Q. I want you to be able to get out whatever information you think is important, but I also would like to be able to get answers to my questions, and I think everybody would like not to be here all day. So if you can carefully listen to my question and try to answer my question, I think that will move things along.
MR. ROCKEY: I object to that, Your Honor.
THE COURT: What's the objection?
MR. ROCKEY: The organization is, argumentative.
THE COURT: Well, there's no question.
One of my difficulties is that I think it's hard

to parse some of this because it's such technical -- so many technical comments. And I think, to be fair, in the scientific community, one can't just look at a heading and kind of ask, Doesn't that mean this, and read a sentence. So I'm not having difficulty with the witness making some explanations. And from what I understand of this, which may not be as much as -- which I know isn't as much as the witness, I think he seems to be staying within the realm of what the question is. So --

MR. LIPSEY: I will obviously defer to the Court.

THE COURT: The point is, I don't think he's being nonresponsive. If you think he's being nonresponsive, you can make that objection, and I'll deal with it. But I haven't really heard him being nonresponsive.

MR. LIPSEY: Okay. I will plow ahead, Your Honor.

BY MR. LIPSEY:

Q. Okay. Would you turn, please, in the same binder to Plaintiff's Trial Exhibit 243, tab 19? And that's a publication by Dr. Biederman and others in 1989; correct?

A. Correct.

Q. And that's something that you reviewed in connection with your work in this case; correct?

A. I did.

Q. And you consider Dr. Biederman to be one of the most prominent clinical pharmacologists in the ADHD field;

correct?

A. That's what it appears to me.

Q. And if you would turn, please, to page 783, in the left-hand column, second-to-last paragraph, first sentence, Dr. Biederman states there: "The pharmacological mechanism of action of DMI -- " -- which is desipramine -- " -- in ADDH remains unknown."

Do you see where I've read?

A. Yes.

Q. And that is Dr. Biederman's statement in 1989; correct?

A. Correct.

Q. Okay. And if you would turn, please, to page 777, the bottom of the right-hand column, Dr. Biederman is there talking about desipramine; correct?

A. Correct.

Q. And he characterizes desipramine's affinity for these other receptors as relatively low compared with other TCAs; correct?

A. Correct.

Q. And the fact of the matter is that desipramine, even though relatively low compared to other TCAs, does have affinity for this constellation of receptors discussed here.

A. Absolutely, as you showed in your opening statement.

Q. And I gather you had occasion to study as many of

Dr. Biederman's publications as you thought was appropriate in the course of preparing your expert report; is that right?

A. I studied a large number.

Q. And there was no limitation placed on you in term of anybody else's publications that you could have reviewed in doing that work; --

A. No.

Q. -- right?

A. Correct.

Q. And in the course of your work, you did not see any publication in which Dr. Biederman or his group suggested using tomoxetine to treat ADHD prior to January of 1995; correct?

A. Correct.

Q. And indeed, you did not find a publication of any group suggesting that tomoxetine should be used to treat ADHD prior to January of 1995; correct?

A. Specifically to tomoxetine, no. But as I said, I think the literature suggested using a drug like tomoxetine.

Q. You talked about a drug called tandamine in your expert report. Do you remember?

A. I mentioned it, yes.

Q. And I think you suggested that tandamine was described in the literature as a selective norepinephrine reuptake

inhibitor.

MR. ROCKEY: Objection, Your Honor; beyond the scope of the direct.

THE COURT: No, no, no. This is an expert. I'm going to let him testify. Otherwise I'd be forced to have counsel call him back in his own case --

MR. ROCKEY: Thank you, Your Honor.

THE COURT: -- and just waste a lot of time. No, I'm going to let him go. It's in his expert report.

Q. I'll reask the question.

You characterize tandamine as having been described in the literature as a selective norepinephrine reuptake inhibitor; correct?

A. Similar in nature to desipramine, perhaps, yes.

Q. And, in fact, it had been disclosed in the literature even before tomoxetine had; correct?

A. Yes.

Q. But you didn't find any suggestion in the literature you reviewed to use tandamine to treat ADHD; correct?

A. Correct.

Q. And tandamine is a structurally very different molecule from tomoxetine; correct?

A. I assume so.

Q. And the fact that tandamine might have been used as an antidepressant does not help you answer the question of

whether it would have been obvious to use tomoxetine to treat ADHD; correct?

A. No.

Q. No, that's not correct?

A. No, it's -- you are correct in your statement. Thank you.

Q. Thank you.

Now, before we leave Biederman 1989, Defendant's Trial Exhibit 20, if we could go to page 782, please, in the right-hand column, in the first complete paragraph, about six lines down, there's a discussion of imipramine. Do you see that? It starts: "Quinn and Rapoport have noted that imipramine, though indistinguishable from the stimulants during the initial phase of treatment, failed to have sustained clinical efficacy in a substantial proportion of children given relatively low doses of that tertiary-amine TCA." Do you see where I've read?

A. Yes.

Q. And that's reflecting an observation made in an ADHD trial of a dropoff in the therapeutic effect with this tricyclic antidepressant; correct?

A. In this study, with that tricyclic, yes, although I believe other studies with other tricyclics and maybe even imipramine suggest it is a sustained, but it's outside my area of expertise.

Q. And in this study, this Biederman 1989 study, Defendant's Trial Exhibit 20, Dr. Biederman observed a delayed response using desipramine; correct?

A. I'd have to look at the observations.

Q. And it's on that same page in the left-hand column.

A. And which page is that? I was just letting you --

Q. Page 782, in the left-hand column, the last complete paragraph, he observed there: "The present study required 3 to 4 weeks to reach a significant drug versus placebo difference in benefits," citing Figure 1. "This slow response, even to a maximum daily dose of desipramine, appears to be inconsistent with previous reports of a more rapid response to imipramine -- " --

Do you see where I've read?

A. Yes.

Q. -- " -- or DMI." Correct?

A. Yes. I think later they speculate about why that might be.

Q. Now let's go ahead and deal with that.

Biederman here says that he saw significant results after three to four weeks; correct?

A. He did. I think the design of the study, though I'd have to look at the methods, was that they wanted to start out with low doses to try to avoid some of the side effects, and they speculated, if I remember rightly, they speculated

that because they started with low doses and they worked their way up slowly, it took a longer time than Donnelly observed.

Q. Okay. If we look at page 780 in the Biederman 1989, Defendant's Trial Exhibit 20, in the left-hand column, first complete paragraph, he gives you the daily doses there. Do you see that?

A. Yes.

Q. And at the end of week one, the dose was 1.8 milligrams per kilogram, and at the end of week two, it was 3.0 milligrams per kilogram; correct?

A. Okay.

Q. And if we go back to the Donnelly study, which is the comparator he mentions back on page 782, which is at tab 17, Defendant's Trial Exhibit 23, and there, they say they got effects on the third day. Do you remember that?

A. Yes. And I think that was the first day they measured, but again, I don't remember the details.

Q. And if we look at page 75 of the Donnelly article, Defendant's Trial Exhibit 23, the average dose on day three in that study was 1.83 milligrams per kilogram; right?

A. Okay.

Q. And that's roughly the dose at week one in Biederman; right?

A. Yes.

Q. And that's lower than the dose in week two in Biederman; right?

A. Yes.

Q. And Biederman did not see a statistical significance until week three; right?

A. Okay.

Q. If you turn, please, in this same volume to tab 14, that's the 1985 Baldessarini work, Defendant's Trial Exhibit 18, on antidepressant agents; correct?

A. Tab 14, yes.

Q. And that's something you considered in preparing your report; correct?

A. Correct.

Q. And if you turn to page 233, he gives the summary and conclusions. And in the first paragraph --

A. Wait. Wait, please.

Q. Excuse me. It's a big article.

A. Yes.

Q. In the last two sentences of that first paragraph, he writes in his "Summary and Conclusions": "In addition to blocking the uptake of norepinephrine, the tricyclic-type antidepressants exert complex effects on the metabolism, receptors, and functions of monoamines in the brain. It is unfortunate that the drugs used to treat patients at increased risk of suicide are so toxic and potentially

lethal."

Do you see where I've read?

A. Yes.

Q. And you recognize Dr. Baldessarini as an authority on antidepressants?

A. I do.

Q. Okay.

A. And I think that's consistent with what I was saying about side effects and the like.

Q. Well, I mean, one of the problems of the tricyclic antidepressants was, the toxic dose was relatively close to the therapeutic dose; correct?

A. That's correct. Well, I think -- I have heard that. Do I know that definitively? I don't.

Q. And a big problem with them is that people could commit suicide with that drug. If they took a lot of pills, they could kill themselves; correct?

A. Yeah, I don't know about that. That I heard that more with the monoamine oxidase inhibitors, but --

Q. Okay. One of the things that tricyclic antidepressants did was, they had effects on conduction in the heart; right?

A. I believe that's true, yes.

Q. Now, in connection with your consideration of the state of the art in 1995, you took into account the side

effects associated with the use of tricyclics to treat ADHD; correct?

A. I did.

Q. Including the cardiovascular side effects; correct?

A. Yes.

Q. And when you think of cardiovascular side effects, you were thinking of effects on cardiovascular function such as those measured by an electrocardiogram; right?

A. That would be one of them. I'm not a clinician, so I don't really know the full manifestation of cardiac effects, or cardiovascular effects.

Q. And you are aware that some patients treated with desipramine for ADHD suffered sudden death; correct?

A. I am aware that a small number of patients did have sudden death while on desipramine, yes.

Q. Okay. But you didn't take into account the sudden-death issue concerning desipramine in deciding whether or not the use of tomoxetine to treat ADHD would have been obvious in January of 1995; correct?

A. Can you repeat that?

Q. Sure.

You did not take into account the sudden-death issue concerning desipramine in deciding whether or not the use of tomoxetine to treat ADHD would have been obvious in January of 1995; correct?

A. I did take into account the fact that there were a small number of sudden-death reports.

Q. Do you have your deposition there, Volume 2?

Starting at page 99, line 25, you were asked --

THE COURT: Hold on.

A. One second. One second.

THE COURT: Page 99.

Q. Page 99, and it extends over to 100, starting at the very bottom of the page, line 25.

You were asked:

"Did you take into account the sudden death issue concerning desipramine in deciding whether or not the use of atomoxetine to treat ADHD was obvious in January of 1995, or did you discount it?

"ANSWER: When I viewed the literature as teaching that a selective norepinephrine reuptake inhibitor that had fewer receptor actions would be useful in the treatment of ADHD, I didn't see the sudden death issue as related to that line of thought."

That was the testimony you gave then; correct?

MR. ROCKEY: Your Honor, can we read on?

THE COURT: One second.

A. You asked did I take it into account. And I took it into account, and then I discounted it. And I'd be happy to explain why.

Q. Well, you did discount it; correct?
A. Yes.
Q. And I think you said yourself you were not a clinician; correct?
A. Correct. But I think I have the scientific training that would allow one to evaluate that issue, as I think I went into detail in my deposition.
Q. Have you ever diagnosed a heart patient?
A. No, I have no clinical experience. But I do know how to look at data and interpret them.
Q. If someone came to you and said, I want to give your child a medication which has suddenly and without explanation killed a number of other children, albeit small, would you feel competent to evaluate that data and decide whether to give the medicine to your child?
A. Well, there are two parts of my answer to that question. First, you said it killed -- well, it's all one answer. You said it killed -- the medication killed the children. In the case of desipramine, it was a very small number. People do, unfortunately, die under any number of conditions and during any number of treatments. And when I looked at the broad literature related to tricyclics and the use of -- and psychostimulants in the use of ADHD, on the one hand, we had a number of cases, a small number of cases of sudden death with desipramine. On the other hand,

psychostimulants block norepinephrine reuptake. Others, tricyclics block norepinephrine reuptake, including nortriptyline. Across the whole range of drugs, there wasn't any consistent reports of sudden death, and my conclusion then and I think it would be true if it were even my own child was that it was more likely a statistical phenomenon rather than a causal correlation.

Q. You would feel competent to make that medical judgment.

A. Yeah. We're talking about numbers and how you analyze numbers and consider the statistical significance.

Q. Numbers mean one thing when it's somebody else's child; it's something else altogether when it's yours. Would you agree?

A. No, we see these reports in the newspapers all the time, when this drug is associated with this side effect or this condition or outcome, but what gets lost in the newspaper article but what us scientists know is really going on is that coincidences occur, and that's why we do statistical analyses, to try to control for the fact that coincidences occur. I feel pretty adequately -- adequately trained that I can assess whether three cases out of some number of kids treated with this drug but also other kids treated with related drugs might be linked to the sudden death.

Q. Okay. You never confronted that issue with respect to desipramine prior to January of 1995; correct?

A. No, sir.

Q. All right.

And prior to January of 1995, there were reports in the medical literature about instances of sudden death of children on desipramine; correct?

A. That is true. I think that's also true for atomoxetine.

Q. The clinical pharmacology and therapeutic use -- strike that.

The therapeutic uses of atomoxetine are beyond your field of expertise; correct?

A. Correct.

Q. Thank you.

Now, would you turn, please, to tab 25 in the same volume, Plaintiff's Trial Exhibit 635?

A. Tab 25?

Q. Tab 25, Plaintiff's Exhibit 635.

Do you have that?

A. Yes.

Q. And that's a publication by Dr. Riddle --

A. Yes.

Q. -- relating to the sudden-death issue with desipramine; correct?

A. Correct.
Q. You considered some of Dr. Riddle's publications on this issue in the course of preparing your expert report?
A. I considered a number of articles that dealt with the sudden-death issue, and Dr. Riddle's was one of them.
Q. And would you turn, please, to page 795?
And in the left-hand column, about eight lines down, there's a sentence that begins: "It is possible..." It's right there.
A. Yes.
Q. And Dr. Riddle states here: "It is possible desipramine differs from other tricyclics in ways that make it potentially more lethal. This possibility is supported by the findings of a recent study indicating that the chance of death after an overdose is greater for desipramine than for other tricyclic drugs," citing Kapur.
A. Yes.
Q. "Desipramine's most distinctive feature among the class of tricyclic drugs is that it is the most specific inhibitor of uptake of norepinephrine."
Do you see where I've read?
A. Yes.
Q. And if it were perceived that the specificity of norepinephrine reuptake inhibition was a problem for this cardiac issue, that would have dissuaded a person of

ordinary skill in the art from trying to use tomoxetine for ADHD; correct?

A. Can you repeat that?

Q. Certainly.

If the perception were that the selectivity of norepinephrine reuptake inhibition was a contributing factor to the sudden-death issue, that would have dissuaded a person of ordinary skill in the art from developing tomoxetine for use as an ADHD medication; correct?

A. I believe there was certainly concern about that, but the data argued against that interpretation. Imipramine is converted to desipramine. Nortriptyline was used, and that's a significant norepinephrine blocker. Stimulants block norepinephrine. I think the bulk of the data, though -- you know, I understand why they're speculating about it, but it is speculation, and the bulk of the data would lead someone skilled in the art, I believe, to conclude that it could just be that desipramine actions and the sudden deaths were unrelated.

Q. I'm sorry, that what?

A. That the relationship between desipramine and the sudden death was not a direct connection.

Q. But Dr. Riddle here confronting the actual issue in 1993 suggests the possibility that the selectivity of desipramine's norepinephrine reuptake inhibition may be a

factor; correct?
A. There is no doubt that there was lots of concern about that, and people switched to other tricyclics which also block norepinephrine reuptake. So it never made much sense to me.
Q. And those other tricyclics also blocked serotonin reuptake; correct?
A. Some of them. Nortriptyline did not.
Q. It blocked serotonin reuptake more than desipramine did; correct?
A. Relatively speaking, I would disagree. Nortriptyline is described in -- the data that I showed in my direct questioning would show that nortriptyline is almost pretty -- it's as selective as desipramine, and that's how it's commonly described.
Q. The operative word is "almost"?
A. No, I'll be happy to go through those data and show you why they're exactly the same.
Q. I thought the thesis of your whole opinion when you stood up here this morning was that desipramine was the most selective norepinephrine reuptake inhibitor among the tricyclics and that's why it was obvious to try to do the same thing. Are you changing your opinion?
A. No, I didn't say it was the most selective among all the tricyclics. I said it was selective and that it is

effective in the treatment of ADHD. When I was talking about those numbers in the column, I had mentioned it's really a ratio thing, and if you look at the numbers for nortriptyline, I think it's 2.2 for norepinephrine and then a very large number for serotonin and dopamine. And so the ratio, they're going to differ a little bit between desipramine and nortriptyline, but it's very similar.

Q. The fact of the matter is, this sudden cardiac death issue scared people into using things other than DMI; correct?

A. It definitely did.

Q. And by DMI, you understood I meant desipramine?

A. Desipramine.

Q. It's an acronym for des-methyl imipramine, which is why it gets used.

And part of your thesis is that tomoxetine is just as selective a norepinephrine reuptake inhibitor as desipramine; correct?

A. Without the receptor interactions.

Q. I would like to show you an article marked for identification as Defendants' Trial Exhibit 137, which is a Biederman article from March of 1995.

And this is an article by Dr. Biederman dealing with the sudden-death issue in relation to desipramine; correct?

A. Okay. Yes. I did not review this one, since it happened prior -- after 1995.

Q. But you do recognize Dr. Biederman as a reliable authority on this issue.

A. Yes. And prior to 1995, it was his opinion that desipramine probably wasn't causally related to the sudden deaths.

Q. And if you turn to page 90 of Defendants' Trial Exhibit 137, in the lower left-hand corner, introductory clause of that paragraph, Dr. Biederman referred to the --

A. I'm sorry, which paragraph?

Q. The bottom, incomplete paragraph on the left-hand column.

A. Okay.

Q. The introductory clause there in relation to this issue says, "Although a current source of grave concern." Correct?

A. Yes.

Q. And if you turn to page 91, in the second complete paragraph, the last sentence, starting "This issue," Dr. Biederman wrote: "This issue may be particularly relevant for desipramine-treated children because of the known effects of desipramine on neuronal reuptake of norepinephrine and epinephrine."

That's what he wrote in 1995; correct?

A. Yes.
Q. Why don't we take a look at the Mefford and Potter article, which is at tab 20, Defendants' Trial Exhibit 61.
That doesn't sound right.
A. It is 20.
Q. No, that is right. Sorry.
The Mefford and Potter article, Defendants' Trial Exhibit 61, is one of the publications you considered in preparing your report; correct?
A. Correct.
Q. These authors were also from Dr. Rapoport's group at the NIMH that did much of the work on ADHD; correct?
A. I don't know if they were part of Dr. Rapoport's group, but they certainly worked in the same area.
Q. Now, Mefford and Potter's theory was that in order to reduce the amount of LC firing, you needed to have more epinephrine; right?
A. Can you repeat that? I couldn't hear the last phrase.
Q. I'm sorry.
Mefford and Potter's theory was that in order to reduce the amount of LC firing in ADHD, you needed to have norepinephrine; right?
A. Yes.
Q. Not -- yes, not norepinephrine, epinephrine.
A. Epinephrine. That is their theory. They're

speculating on circuitry involved in how the drug works, which is different than pharmacology.

Q. If you turn, please, to page 38, the right-hand column, first full paragraph states, starting "Based," "Based on these arguments, the ideal therapeutic agent for treatment of hyperactivity would show a high degree of specificity for uptake into noradrenergic terminals and storage vesicles, and possess potent inhibitor properties toward MAO type A..."

Do you see where I've read?

A. I do.

Q. Now, tomoxetine does not show a high degree of specificity for uptake into the noradrenergic terminals and storage vesicles; correct?

A. That's correct. Nor does desipramine.

Q. And tomoxetine does not possess potent and inhibitory properties toward MAO type A; correct?

A. That is correct. Nor does desipramine.

Q. So this suggestion by Mefford and Potter is not a suggestion to use tomoxetine; correct?

A. This suggestion is based on a speculated mechanism of how a pharmacological action then triggers a series of biological events that lead to therapy.

Q. Tomoxetine is not Mefford and Potter's ideal therapeutic agent; correct?

A. Correct.

THE COURT: Counsel, how much longer are you going to be?

MR. LIPSEY: I'm sorry?

THE COURT: How much longer are you going to be?

MR. LIPSEY: A while.

THE COURT: Do you think this would be a good time to take a break, an afternoon break?

MR. LIPSEY: I would love a break.

THE COURT: Why don't we take 15 minutes, and then we'll come back and finish up for the day.

You can step down.

THE WITNESS: Thank you.

(Recess taken)

THE COURT: Be seated.

(The witness resumed the stand.)

THE COURT: Continue.

BY MR. LIPSEY:

Q. Welcome back.

MR. LIPSEY: It's blessedly cool out in the hallway, Your Honor.

THE COURT: For those of you who want to take your jackets off, feel free to do so.

MR. LIPSEY: Your Honor, bless you.

(Laughter)

THE COURT: Well, if anybody asked, I would have --

(Laughter)

THE COURT: I want to limit it to jackets.

(Laughter)

THE COURT: Okay.

MR. LIPSEY: Thank you.

BY MR. LIPSEY:

Q. With the blessed leave of court, we are here now, Dr. Berridge, in our shirt-sleeves. Hopefully it will be a facilitator of communication.

When we broke, we are were talking about Mefford and Potter, Defendants' Trial Exhibit 61, which is at tab 20 of the binder, and we were on page 38, looking at the characteristics of what Mefford and Potter characterized as their ideal therapeutic agent for the treatment of ADHD, and we had gotten through the first one.

Next, he states, starting with the word "Even": "Even more ideal would be selectivity towards brainstem PNMT-containing neurons." Do you see where I've read?

A. Yes.

Q. Okay. And that's not tomoxetine, either; correct?

A. There are no drugs that do that that are selective to those neurons.

Q. So tomoxetine is not the drug described here by

Mefford and Potter as even more ideal; correct?
A. Based on their hypothesis about circuitry involved, correct.
Q. And the last proposal he makes, he says: "Alternatively, a site selective alpha-2 agonist acting only at the brainstem level might be effective and perhaps devoid of growth hormone effects."
Do you see where I've read?
A. I do.
Q. Okay. And that is not tomoxetine either; correct?
A. Nor desipramine. But yes, you're right.
Q. And indeed, tomoxetine would never be confused for an alpha-2 agonist because what distinguishes tomoxetine from other drugs is its lack of binding to receptors; correct?
A. That is correct, but it does act as an indirect alpha-2 agonist because it stimulates -- elevates norepinephrine to stimulate alpha-2 receptors.
Q. Atomoxetine does not bind to the alpha-2 receptor; correct?
A. That's correct.
Q. And therefore, it is not an alpha-2 agonist within the meaning of this statement; correct?
A. Correct.
Q. Now, to the extent that tomoxetine may inhibit reuptake of norepinephrine and thereby raise norepinephrine

concentrations in the synapse, it would be expected to stimulate interaction of norepinephrine with all the available neurotransmitters -- excuse me, all the available receptors, not just the alpha-2 receptors; correct?

A. That's correct.

Q. And particularly not just alpha-2A receptors; correct?

A. That's correct.

Q. Okay. Let's take a look at McCracken, Plaintiff's Trial Exhibit 5 at tab 21.

THE COURT: I'm sorry. What was that tab?

MR. LIPSEY: Tab 21, the next one in order, Your Honor.

Q. Okay. The McCracken reference is something you reviewed in preparing your report; correct?

A. I don't remember. I certainly have read it.

Q. And you know Dr. McCracken and recognize him as a reliable authority on ADHD; correct?

A. Yes, on the clinical side.

Q. Okay. And in fact, you've published articles with him; right?

A. I have. I'm a co-author on one article.

Q. And he was at the NIMH with Drs. Rapoport and Zametkin; correct?

A. I will believe that.

Q. Okay. Now, if you turn to page 208, please, this is

in his summary section, and specifically the third sentence, he states: "It is proposed that maximal benefit from medications for ADHD symptom amelioration occurs only when inhibitory presynaptic DA agonism and alpha-2 adrenergic effects denominate, leading to reduction in ascending Mesolimbic DA inhibition and reduced L-NE activity, respectively." Do you see where I've read?

A. Yes. He like Mefford and Potter in this part of the paper was speculating on neurocircuitry involved in pharmacological treatment of ADHD.

Q. Okay. So the first property he mentions is one that would affect the level of dopamine; correct?

A. Correct.

Q. And the second part he mentions would decrease norepinephrine in the LC; correct?

A. Correct. And this is in the context of how you get optimal effects, so he's comparing this to the psychostimulants.

Q. And in the last paragraph of the summary, he states, in the sentence that begins: "For example, this model would predict that B-HT 920, a selective DA autoreceptor agonist drug that also possesses alpha-2 adrenergic agonist properties, would have equivalent efficacy to the stimulants within appropriate dosage ranges."

Do you see where I've read?

A. Yes.
Q. And that doesn't describe tomoxetine either; correct?
A. That does not. Nor does it describe desipramine.
Q. And, in fact, tomoxetine does not satisfy the two-part model that --
A. No. It's a model, and it does not satisfy it.
Q. And let me just get a complete question so we have a record.

Tomoxetine does not satisfy the two-part model proposed by Mefford and Potter in the summary; correct?
A. Correct.
Q. And before we leave McCracken, if we can go back to the beginning, page 201, in the left-hand column, about six lines up from the bottom, he states, in part: "As yet there is no consensus on the precise mechanism of action of ADHD's most commonly prescribed treatment (the stimulants) or of the etiology of ADHD itself." Do you see where I've read?
A. Yes.
Q. And you would agree with that; right?
A. That's an accurate statement.
Q. Would you turn, please, to page 204?

In the right-hand column there, he's talking about monoamine oxidase inhibitors, MAOs -- MAOIs, excuse me. The very last sentence of that paragraph, he states: "However, because of the requirement of dietary restrictions and

possible side effects, the MAOIs remain primarily of interest as research treatments and are prescribed only in rare circumstances."

Do you see where I've read?

A. Yes.

Q. And you would agree with that also.

A. Yes. I said that earlier.

Q. And in the next paragraph there on page 204, he's talking about the tricyclic antidepressants, particularly desipramine and imipramine; correct?

A. Yes.

Q. And in the second sentence, he notes that some investigators have noted a falloff in response with those drugs even during eight-week drug trials; correct?

A. He does say that, yes.

Q. He goes on to state that the biggest disappointment with the tricyclics for ADHD is in their consistent lack of effectiveness in enhancing cognition; correct?

A. That's true, and he's referring to in laboratory tests, not in the clinical setting.

Q. That's your interpretation of what he's written there.

A. No, I'm pretty sure that's accurate.

He also lists tricyclics as the second line of treatment under some conditions in a different part of that paper, including desipramine.

Q. And before we leave, if you would quickly flip back to page 205, in the right-hand column, there's a discussion of clonidine, and up at the top, the second complete sentence, he states: "Clinical experience has suggested -- " -- with respect to Clonidine -- " -- that the 'therapeutic window' of behavioral effects without excessive sedation is narrow."

And you would agree with that; correct?

A. I wouldn't disagree with that. I don't have the expertise to know.

Q. Let's take a look at the Shenker review article, which is Plaintiff's Trial Exhibit 6 in tab 23, skipping one.

And this is an article you reviewed in connection with your work on this case; correct?

A. Yes.

Q. And it's basically a review of the mechanism of action in terms of treatment of ADHD; correct?

A. Yes.

Q. And the author here, Andrew Shenker, is both an M.D. and a Ph.D.; correct?

A. Yes.

Q. If you turn to the back of the article, page 364, let's look at the acknowledgments, you see he gratefully acknowledges the comments of Dr. Rapoport, Dr. Zametkin, and Dr. Potter that we've talked about before for their comments on an earlier version of the manuscript. Do you see that?

A. Yes.
Q. That was the group at NIMH; right?
A. Yes.
Q. Now, by my count, you've cited this article a total of 12 times in the two expert reports you've prepared in connection with this litigation.
A. I find this a very knowledgeable article.
Q. I'm sorry?
A. I find this a very knowledgeable article. It seems to be well informed.
Q. Okay. If we could go to page 340, please, there's a section there in Shenker where he's discussing the tricyclic antidepressants; correct?
A. Correct.
Q. And he's got a general discussion of them and their actions on page 340, and then it extends over on to page 341; correct?
A. Correct.
Q. And the first paragraph of page 341 states: "Any discussion of the efficacy of imipramine and desipramine in ADHD must include the fact that, unlike amphetamine, they are fairly potent antagonists at the alpha-1 AR and certain other brain receptors. Whether these properties contribute to or detract from clinical efficacy remains to be seen."
Do you see where I've read?

A. Yes.
Q. And the experiment to answer that question had not been done by January of 1995; correct?
A. The experiment to definitively answer that question had not been done. There certainly were many observations in the literature related to that, which would suggest that those receptor actions are unlikely to contribute in a substantial way to the effects, therapeutic effects of the tricyclic.
Q. Shenker addressing a problem in the field in 1992 stated: "Whether these properties contribute to or detract from clinical efficacy remains to be seen." That's what he wrote at the time; right?
A. That's what he wrote, and that is not inaccurate.
Q. Now, would you turn, please, to table three at page 359?
A. Okay.
Q. You're better at getting to it than I am.
A. Once in a while.
Q. That table is entitled "Selective Drugs That May Be Useful in Behavioral Research on ADHD"; correct?
A. Correct.
Q. There are 25 drugs listed there; right?
A. Correct.
Q. And none of them is tomoxetine; correct?

A. None of them is tomoxetine.
Q. And none of them is a selective norepinephrine reuptake inhibitor.
A. That's correct. That's because this paper is focused on how do you mimic the optimal or maximal efficacy of stimulants, and as I said, we already know that selective norepinephrine reuptake inhibitors aren't as effective as the stimulants. So you wouldn't list them on a table that suggests where you might go to get comparable efficacy to the stimulants. There is a context here.
Q. None of those drugs is a selective norepinephrine reuptake inhibitor.
A. That's correct.
Q. To the extent he's got uptake inhibitors at all, they are either dopamine uptake inhibitors or mixed norepinephrine and dopamine uptake inhibitors; correct?
A. On this table, that's correct.
Q. Turn back to page 356 on Plaintiff's Trial Exhibit 6. It's got a section there on "Future Research." Do you see that?
A. Yes.
Q. Under the first heading there on page 356, which we'll do the old-fashioned way, is entitled "Future Research," and the first heading is "New Drugs." Do you see that?
A. I do.

Q. And he states, first of all, "It" may very well be that increased synaptic availability of both dopamine and norepinephrine is required for optimal pharmacotherapy of ADHD."

A. Yes, and that comes from the psychostimulants.

Q. I'm sorry?

A. That conclusion comes from the psychostimulants.

Q. And in the next paragraph, he mentions the drug Nomifensine; correct?

A. Correct.

Q. And Nomifensine was a mixed uptake inhibitor for dopamine and norepinephrine.

A. Correct.

Q. And unfortunately, it was found to have toxic effects when actually used; correct?

A. Yes, as happens in drug discovery and drug development programs.

Q. Okay. And that's why you always have to test it in humans to know whether it will work; right?

A. Absolutely.

Q. I'm sorry?

A. Yes.

Q. And he goes on, Shenker goes on here at page 356 to state: "But several new drugs that are potent blockers of both dopamine and norepinephrine uptake systems have been

described," and he names a few.
A. Yes.
Q. And tomoxetine is not such a drug.
A. No, because it wouldn't be expected to increase dopamine and norepinephrine simultaneously.
Q. Would you turn, please, to page 358? I'm sorry, 357, and about two-thirds of the way down in that first incomplete paragraph, Shenker states: "In treating some neuropsychiatric disorders, the more successful drugs may be those that are less selective, or those that can alter the integration of complex neurotransmitter systems."
Do you see that?
A. Yes.
Q. And tomoxetine was decidedly selective; right?
A. Correct.
Q. And if you turn to page 358, the last incomplete paragraph, first line in the section under "Animal Research," Shenker states there that "a phrmacologic model to explain drug efficacy in ADHD may be years away"; correct?
A. I'm sorry, I thought you were going to highlight that.
Q. Oh.
A. Can you repeat what it says?
Q. Okay. The sentence beginning "Although," he states that "a pharmacologic model to explain drug efficacy in ADHD

may be years away"; correct?
A. I don't see it, but I won't dispute that it's there.
Q. Well, even I don't want you to guess.
(Laughter)
Q. I'm sorry, it's above "Animal Research." That's where we want to focus.
A. Oh, yes. Now I see.
Q. "Although a pharmacologic model to explain drug efficacy in ADHD may be years away"; that's what he said there in 1992, right?
A. Yes, and I believe that's accurate today.
Q. And if you go to page 364, the first complete paragraph, he states again, "a simple pharmacologic model to explain the utility of stimulants, tricyclics, MAO inhibitors, neuroleptics and clonidine in ADHD is not yet available." That is what he said at the time; correct?
A. I think that is in reference to a model that would explain how they're all effective, and I think that's true.
Q. Now, to back up to a topic that we touched on before, one of the real problems confronting both the underlying neuroscience in humans and the development of new drugs was the inability to take direct measurements in the brain of a living human being; correct?
A. I don't know if I would agree with that statement that it was a -- can you repeat it?

Q. One of the impediments both to a complete understanding of the neuroscience and to the development of drugs to treat ADHD was the inability to take measurements directly in the living human brain; correct?

A. I would agree with the first part, that we couldn't understand the neuroscience without that. I wouldn't agree to the second part, that you would need that to develop drugs.

Q. You don't think an understanding of what's going on inside the human brain is relevant to the design of drugs?

A. We -- we in the generic sense have been developing drugs to treat human disorders for more than a half a century. In that period of time, we've never been able to measure what's going on in the brain.

Q. Okay, and that's really the point I want to get to. You can measure it in humans -- in rats; right?

A. And that has served pretty well.

Q. Okay, and the way you have attempted to get at that in rats is by inserting probes into the brain of a living rat, presumably.

A. And humans.

Q. H'm?

A. And humans. That approach, inserting a probe in the brain of rats, has been used in humans.

Q. Okay. But there are ethical constraints --

A. There are, that's right. You'd have to -- it's a unique population of humans where that would happen.
Q. Okay.
THE COURT: Glad to hear that.
(Laughter)
MR. LIPSEY: Only lawyers, Your Honor.
(Laughter)
Q. And there are ethical concerns about doing surgery on a person with ADHD; correct?
A. Correct.
Q. And in fact, there are FDA regulations regarding the types of human experimentation that could be done; correct?
A. Correct.
Q. And those regulations require that the experiment be approved by an Institutional Review Board; correct?
A. Yes.
Q. And the Institutional Review Board can't approve the experiment until the risk is reasonable in relation to the anticipated benefits to the patient; correct?
A. I don't know about that. I've never served on a human subjects internal review board. I have served on panels for animals. My understanding is that -- and this is true in animals -- you just want to make sure that whatever is happening proceeds in some -- to match some ethical standards.

Q. Okay. And --
A. I'm not sure that people -- and I don't know how it works in humans, so I guess I don't know the answer to your question.
Q. Okay. But with animals, you don't need informed consent, and with people, you do; right?
A. Correct.
Q. And part of getting informed consent in accordance with the FDA regulatory framework is informing the patient of benefits that reasonably may be expected from the procedure; correct?
A. I'll take your word for it. Again, I have no experience with human subjects IRBs.
Q. Let's talk a little bit about this issue which has been various characterized as an enablement issue or utility issue or some hybrid of the two.

I gather you have offered the opinion that a person of ordinary skill in the art informed of this invention would perceive it as being one that was reasonably likely to work; is that right?
A. Based on the prior art, correct.
Q. So I'd like to ask you a hypothetical question, and it's a lengthy hypothetical question, so I'm going to break it into bite size pieces. All right?
A. Please.

Q. First, I'd like you to assume that persons of ordinary skill in the ADHD art in January of 1995 were not looking for a selective norepinephrine reuptake inhibitor, but instead were looking for drugs with combined effects on dopamine and norepinephrine, or drugs that directly bound to receptors, or drugs that had selective influences on some adrenergic receptors but not others. Do you have that much in mind?

A. We're looking for drugs that would do many things. Is that right?

Q. Right, that they were looking for basically multifunctional drugs or drugs that actively bound to a receptor.

A. Okay.

Q. Okay? So you've got that much in mind.

I'd like you to assume further that the idea of a selective norepinephrine reuptake inhibitor was no longer of interest for ADHD because of sudden-death issues with desipramine, but not with other TCAs where the principal difference between the two was the relative selectivity of desipramine for inhibiting norepinephrine reuptake.

Do you have that much in mind?

A. Okay.

Q. And I'd like you to assume in that environment that an experienced scientist came to such a person of ordinary

skill in the art and said, stop what you're thinking, stop thinking that, and think about this: I have a highly selective norepinephrine reuptake inhibitor with basically no activity towards other receptors. I have done an experiment in a thousand people, and I have determined that it's notably safe. I believe it will work in ADHD and that that safety will be a benefit there. I believe it will be effective in ADHD at doses between five milligrams and 100 milligrams a day.

Do you have that much of my hypothetical in mind?

A. I do.

Q. With that in mind, and with the aid of hindsight, and reviewing the prior art with this suggestion in mind, would a person of ordinary skill in the art in January of 1995 have viewed the idea that tomoxetine could be used to treat ADHD as incredible?

A. As being credible or --

Q. Incredible.

A. Well, if we go with all of those assumptions, which I don't believe accurately reflects what was happening in 1995, I think the answer would be yes.

Q. And would a person so skilled have accepted that the treatment with tomoxetine could work?

A. I don't know.

Q. And why is that?

A. You're making a lot of assumptions there and it's really hard for me to know -- you know, if it were me, and I were that hypothetical person, and I was taking all those assumptions, you know, I guess anything's possible, but --

Q. No, no, my hypothetical --

A. -- but I think the chances are that you would -- based on everything that you said that someone would say it could work, maybe, it may not, it may be likely not to work.

Q. Okay. I didn't ask you to change any of your assumptions about what the prior art taught. I was asking you to change your assumptions about what people skilled in the art were looking for. Do you understand?

A. You're losing me.

Let me try to keep it --

Q. The point being, to try to simplify the hypothetical --

A. So people were looking for the things you said, but we haven't thrown out the prior art?

Q. The prior art is what the prior art is. It includes the invention of fire, the steam engine, and it progresses all the way up until 1995.

A. You know, if I don't throw out the prior art, I look at desipramine and other selective norepinephrine reuptake blockers.

Q. I'm sorry?

A. If I don't throw out the prior art, if I'm allowed to keep the prior art, I would note that desipramine and other norepinephrine reuptake blockers are effective in treating ADHD.

Q. And so had you been a person of ordinary skill in the art studiously working away on the projects of the day that did not include this issue and not have it in mind that somebody came to you and said Stop that, think about this, think about using tomoxetine to treat ADHD, when you stopped and thought about it, and looked back at what you could glean from the prior art in hindsight, I gather you would conclude that it could work.

A. I think at the time a person of ordinary skill in the art, though they might be looking at these multiacting drugs to mimic the efficacy of stimulants, would have to know about tricyclics, including desipramine, and a person of ordinary skill in the art would have to know that it is a selective norepinephrine reuptake inhibitor, and I think everything goes from there.

Q. Your conclusion is?

A. That someone would say yeah, it could work. It may not be as effective as stimulants, but it could work.

Q. Okay. That's what I wanted to know. But in any event, in the hypothetical that I offered, it would not be viewed as incredible; correct?

A. Correct.

Q. Let me ask you a slightly different but equally painfully long hypothetical.

I want you to suppose or assume that a pharmaceutical company with 20 years of experience with monoamine reuptake inhibitors and antidepressants came to you and said, We have tomoxetine, a highly selective norepinephrine reuptake inhibitor, virtually devoid of activity in other receptors. We have tested it in a thousand human patients, and we have noted it to be notably safe. The Massachusetts General Hospital IRB and the Food and Drug Administration have approved a clinical trial in humans of the drug for ADHD. The patients have been notified by the IRB that a benefit that reasonably may be expected is that their ADHD symptoms may improve if they're on tomoxetine. We believe that it can be used to treat ADHD.

Under those circumstances, by viewing that suggestion with hindsight and gleaning from the prior art what could be gleaned on the issue, in your opinion, would a person of ordinary skill in the art view that suggestion to use tomoxetine as incredible?

A. Can you tell me what you mean by -- what's the significance of the phrase, "in hindsight"?

Q. What I'm telling you is, I've asked you to stop

thinking what you're doing -- what you're thinking about now. I want you to stop and think about my idea. I want you to think about my idea, and based on everything that you now can see in the prior art, since I've shone a light on it, can you look at it and say, You know, I think that could work?

A. I don't think you need the hindsight part of your question to answer that question.

Q. But you would agree with me that certainly with hindsight, you could conclude that it could work.

A. I think with hindsight, the conclusion would be the same as it was without hindsight.

Q. That may be as close to agreement as we can get.

Now, you relied on Dr. Heiligenstein's deposition testimony in support of your opinion that you felt that without the prior art, there was no way to believe that this would work; correct?

A. Correct.

Q. What Dr. Heiligenstein testified to is, he didn't have any data, he didn't have any tomoxetine data on the issue of whether it would work for ADHD; right?

A. Correct.

Q. And he basically said that he wasn't going to be satisfied that it could work until he got data; right?

A. Correct.

Q. And he was not satisfied even with the data from the study Dr. Biederman did; right?
A. Correct.
Q. And, in fact, he testified at his deposition that he wasn't satisfied until he had the results of the first two double-blind studies sometime in 1997; right?
A. Correct.
Q. Now, those are the kinds of studies that you need in order to actually market the drug with FDA approval; right?
A. I don't know what's required for FDA approval. But you need those kinds of studies to start to have definitive data related to the question.
Q. You need double-blind controlled studies showing safety and efficacy in order to get FDA approval, do you not?
A. Okay.
Q. And that's why drug companies do that kind of stuff; right?
A. Okay.
Q. And so the yardstick that Dr. Heiligenstein was using was one that was much closer to the question of whether the drug could be commercialized or approved than it is to the rudimentary question of whether it could work; right?
MR. ROCKEY: Objection, Your Honor.
THE COURT: What's the objection?

MR. ROCKEY: Mischaracterizes Dr. Heiligenstein's testimony. What he said was, I wasn't sure it would work.

THE COURT: Do you recall what -- what is his name?

THE WITNESS: Heiligenstein.

THE COURT: Do you recall what he said?

THE WITNESS: What I was going to say is, Heiligenstein thought that. He didn't say that. He said, I didn't have data. He didn't say, I have preliminary data, it's not clear, which I would have said, if I were him, and I had preliminary data. He said he didn't have data. And as a scientist, I'm going to interpret that at face value because there was no qualifying statement associated with that.

Q. Okay. After the MGH study, he did have data; right?

A. I -- yes, after the MGH study, he did.

Q. And that still didn't satisfy Dr. Heiligenstein, did it?

A. You know, at that point, I don't remember what he said.

Q. Well let me read his deposition.

This is the Heiligenstein deposition, starting at page 138, line 24, and extending to 139, line 10:

"QUESTION: And I think you also testified that you didn't think that the Mass. General study proved your

hypothesis. Is that correct?

"ANSWER: I was not satisfied, no.

"QUESTION: When did you finally become satisfied?

"ANSWER: It was not until we had data from the first two double-blind studies.

"QUESTION: And do you recall about when that was?

"ANSWER: I don't recall when that data was available.

"QUESTION: Was it after 1997?

"ANSWER: Yes.

A. So there, he's mentioning proving a hypothesis. And I agree with him. You want to prove your hypothesis, which is awfully hard; you need a body of pretty strong data. But if I were to ask, do I have data to support my hypothesis, I would say I have data; it's not definitive, it's preliminary in nature, we need to replicate it. Myself and everyone else I know in the business, we always describe preliminary data because preliminary data are much better than no data.

Q. His testimony was that he, subjectively, wasn't satisfied that the hypothesis had been established until after those two double-blind studies; correct?

A. He said proven. And I think there is a distinction.

Q. Now, I gather you agree that the invention described in the patent, the treatment of ADHD with tomoxetine in doses of five to 100 micrograms per kilogram per day, does,

in fact, work as described.

A. Can you repeat that?

Q. You agree that the invention of using tomoxetine to treat ADHD patients at doses of from five to 100 micrograms -- milligrams per kilogram per day does, in fact, work as described?

A. I'm not familiar with the doses that are used. I do know that atomoxetine has been reported to be effective in the treatment of ADHD.

Q. Okay. Have you seen the label for the product?

A. I may have. I don't remember any of the details.

Q. Okay. And if the label described -- said that the maximum dose was a hundred milligrams a day -- I actually misspoke in my question. Let me ask you a better one.

Let me ask you to assume that the FDA-approved label states that tomoxetine is effective and safe to treat ADHD with a maximum dose of 100 milligrams a day, and that the FDA-approved dosage forms are in amounts ranging from 10 milligrams to 100 milligrams.

Do you have the assumption in mind?

A. Okay.

Q. I gather you would agree that the disclosed invention in the patent to treat ADHD patients with tomoxetine in a dose of from five to 100 milligrams per day does, in fact, work as described.

A. Yes.
Q. And I gather you would agree that the results of the Biederman study showed that tomoxetine was effective in treating ADHD patients.
A. The 1989 paper -- the 1989 study?
Q. No, the 1998 paper describing the study that was done beginning in December of '94 and finished in early 1995.
A. Oh. Right. Sorry. I got confused.
Q. Let me reask the question.
A. I --
Q. Let me just ask it, because it may be important.
Do you agree that the results of the Spencer and Biederman study conducted at MGH in 1994 and early 1995 and ultimately published in an article in 1998 show that tomoxetine is effective to treat ADHD?
A. I'm pretty sure that's what they say. I haven't read that paper in a while. But I know they have a paper that shows it's effective. I don't know -- I know they have a paper that shows it's effective.
Q. It shows what?
A. That the drug atomoxetine is effective.
Q. Now let's talk about the scope and content of the prior art for just a minute.
You did not include as a basis for your opinion prior art relating, for example, to MAO inhibitors; right?

A. I did. I did, I thought.
Q. You did?
A. Yes.
Q. Okay. And you did include specifically prior art relating to the tricyclic antidepressants; right?
A. Yes, among other compounds.
Q. Okay. But you did not include in your analysis of the obviousness issue in your report prior art relating to treatment of urinary incontinence; is that correct?
A. That's correct.
Q. Okay. And that was because you believed that the prior art leading to treatment of urinary incontinence was not scientifically pertinent to the issue of the obviousness of using tomoxetine to treat the disease of ADHD; right?
A. Correct.
Well, --
Q. No, that's fine.
Let's talk for just a minute about the picture that you had up here, I think it's slide eight.
MR. LIPSEY: May we have their slide eight, anybody that's got the machine?
If you can start it up and I'll tell you where to stop it, and then I'd like to ask some questions.
That's not quite the one I was looking for.
MR. ROCKEY: That's an animation. Your Honor,

that's an animation. That's why you don't see anything happening.

MR. LIPSEY: Okay. Go ahead and let it start, and I'll tell you when to stop.

(The animation was played .)

MR. LIPSEY: Okay. Stop it. Can you go back just a little bit?

Okay. Go forward some.

Okay. Go ahead and stop it right there.

Q. Now, that is the schematic illustration that you offered of how a norepinephrine reuptake inhibitor could prevent norepinephrine in the synapse from being taken back up into what you called the presynaptic neuron; correct?

A. Correct.

Q. And the little green triangles there are the norepinephrine reuptake inhibitor; correct?

A. Correct.

Q. And when you have a norepinephrine reuptake inhibitor that can bind not only to the reuptake sites but also to receptors, you could end up with those little green triangles down on the postsynaptic neuron where you've labeled the beta, alpha-2 and alpha-1 receptors; correct?

A. Correct. And we know, as I said, tricyclics do that.

Q. Okay. There are a couple of pieces of prior art that I would like to go through with you. If you could go back

to Volume 4 in your book, and turn, please, to tab 11 and Defendants' Trial Exhibit 32.

A. Volume 4. So now we're out of Volume 5?

Q. Well, we never were -- it's the same volume we've been talking about.

A. All right. Which tab?

Q. Tab 11, the very first one.

A. Yes.

Q. That's a 1982 Lilly publication describing tomoxetine as a selective norepinephrine reuptake inhibitor and pointing out that it was devoid of affinity for receptors; correct?

A. Correct.

Q. If you would turn, please, to tab 13. That's Defendants' Trial Exhibit 55. That's something you considered in forming your opinion; right?

A. I have seen it, yes.

Q. And this reported a preliminary, a very preliminary clinical trial of tomoxetine for depression; correct?

A. Yes.

Q. And that was in 1984; right?

A. Correct.

Q. And by 1995, there had been no report of any successful demonstration of tomoxetine for depression in Phase III trials; correct?

A. I don't know the literature on tomoxetine's use in depression.

Q. Okay. And is it your understanding from your review of the materials in this case that tomoxetine in fact failed to show efficacy in a large clinical trial of depression?

A. I know there was one study that did come to that conclusion. I know I've heard of other comments somewhere in this -- here in this case that it does have antidepressant action. I didn't look into that.

Q. Okay. But as far as you know, it never was approved by the FDA as an antidepressant; correct?

A. That's correct.

Q. And to the extent a person of ordinary skill in the art sees a preliminary report in 1984 and there's still no drug by a decade later, that could tend to suggest there was some problem with the drug; right?

A. Well, it depends on what you mean by there was no drug. If you mean FDA approval, I'm not sure I would agree. I know drugs are used without FDA approval.

Q. I mean, that's a possible inference that could be drawn by persons in drug development would be that if it appeared a drug had entered clinical trials in 1984 and that it disappeared from the face of the earth with no announcement of successful Phase III trials that there was potentially a problem with the drug; correct?

A. Well, someone with experience in drug discovery could reach a number of conclusions, that maybe it wasn't as effective as they wanted, for whatever reason they decided they're going to put their priorities somewhere else. I just don't know enough about this to give you a strong opinion either way.

Q. Yes, but one of the possibilities would be that there was either some toxicity problem or some efficacy problem in the drug; correct?

A. Correct.

Q. Okay. Would you turn, please, to tab 15, and that's the 1985 article that you say referred to the 1983 article.

A. Correct.

Q. And for the record, the Hunt article is Defendants' Trial Exhibit 314, and in this 1985 article, Dr. Hunt describes clonidine as inhibiting norepinephrine release; correct?

A. Yes.

Q. In tab 16, Defendants' Trial Exhibit 59 -- I apologize. That's Dr. Hunt's 1986 article, making the same statement about clonidine; correct?

A. Yes. Again, this was before the idea of postsynaptic alpha-2 receptors modulating cognition had percolated through the field, and as I said, clonidine inhibiting norepinephrine release and being effective in ADHD was

always confusing before we learned about postsynaptic alpha-2 receptors.

Q. Okay. Would you turn, please, to tab 22? And that's Defendants' Trial Exhibit 66. That's the Silver publication relating to variety of ADHD treatments, including clonidine; correct?

A. Correct.

Q. And in this 1992 publication, Silver also reports that clonidine reduces norepinephrine; correct?

A. Correct, and it certainly does.

Q. Would you turn to tab 24, please?

This is Defendants' Trial Exhibit 67. This is the 1992 publication of Dr. Green that we talked about earlier that you cited in your expert report; correct?

A. Correct.

Q. And in this article, Dr. Green also characterizes clonidine as an inhibiting endogenous release of norepinephrine; correct?

A. Yes.

Q. Would you turn, please, to tab 29?

This is Defendants' Trial Exhibit 93, the Cusack publication, that actually measured receptor binding affinities for a variety of drugs in human brain tissue; correct?

A. Um-h'm.

Q. As distinct from the rat brain tissue that had been measured earlier.

A. Yes.

Q. And this was something you considered in forming your opinions; correct?

A. Yes.

Q. And one of the conclusions that Cusack draws here on page 563 in Defendants' Trial Exhibit 93, the right-hand column, at the bottom of the short paragraph beginning with the word "Venlafaxine," Cusack notes: "...from a practical standpoint, there were many other compounds that would not likely affect any of these seven receptors directly in vivo. These compounds included...tomoxetine." Right?

A. I'm still looking for that. Can you give me the directions to it?

Q. On page 563, --

A. Yes.

Q. -- in the middle of the right-hand column, --

A. Okay. Yes.

Q. -- there's a short paragraph that begins with the word "Venlafaxine."

A. Yes.

Q. And at the bottom there, Cusack concludes that based on his data, tomoxetine is unlikely to affect any of these seven receptors directly in vivo; correct?

A. Yes.
Q. And that's in distinction to the classical tricyclic antidepressants which he characterizes a few lines above as being the most potent compounds at blocking five of the seven receptors; right?
A. Correct.
Q. Would you turn, please, to tab 31? And that's Defendants' Trial Exhibit 112, and that's a Lilly article describing a mixed inhibitor of both serotonin and norepinephrine reuptake; correct?
A. Correct.
Q. And that's the drug that ultimately became duloxetine; correct?
A. Yes.
Q. Now, if we could talk briefly about some of the publications that you relied upon in your direct testimony, hopefully up there you still have somewhere your original binder.
A. Somewhere, I do. Yes.
Q. Let's start with Defendants' Trial Exhibit 26, which is the 1985 Gastfriend article. And in the opening paragraph there, Gastfriend notes that "Pharmacologic treatment of attention deficit disorder (ADD) has largely been limited to the use of psychostimulants in prepubertal children. However, as many as 30 percent of children prove

refractory to treatment with stimulants."

And you would agree with that, I gather.

A. I don't know the exact number. I do know that there's some population that proved refractory. Whether it's 20 or 30, I'm not sure.

Q. Okay. But you don't have any information in conflict with what Gastfriend writes here; correct?

A. In general terms, no.

Q. And right below that, he states that "In adolescents, little is known about the nature of the disorder itself, much less about pharmacologic agents for treatment." Correct?

A. Yes.

Q. Could you look, please, at Defendants' Trial Exhibit 22, which is the Bolden and Watson article?

This is a 1993 publication; correct?

A. Correct.

Q. And looking at the first sentence of the article underneath the abstract or summary, after the abstract, the first sentence of the actual article, Bolden and Watson state here: "Antidepressant drugs offer effective treatment for depression, although their mechanism of action in the treatment of depressive illness remains an enigma." Do you see where I've read?

A. Yes.

Q. And I gather you don't quarrel with that?
A. No, in terms of depression use, it's -- it's always complicated, and I think -- in terms of depression use, it's more complicated because you have to treat patients for multiple weeks before you see therapeutic efficacy. So the acute pharmacological actions that I showed here aren't sufficient to explain how these drugs translate to a change -- to a therapeutic effect. It's a little more complicated.
Q. Okay. So let's talk about that a little bit.

Bolden Watson, Defendants' Trial Exhibit 22, does, in fact, hint at that on page 1027 in the last complete paragraph, where he says: "The mechanism of therapeutic effects of antidepressants is uncertain. Possibly, the resulting potentiation of monoaminergic neurotransmission caused by uptake inhibition by antidepressants is a first step in a complex cascade of events ultimately producing a desensitization and downregulation of certain neurotransmitter receptors."

A. Correct.
Q. And that 's the complex phenomenon you were referring to in your last answer.
A. That's some of it, yes.
Q. In fact, it's even more complicated than that.
A. Yes.
Q. And in fact, they can end up affecting other

neurotransmission systems, including serotonin and dopamine; correct?

A. Correct. And that's true with any drug we give that acts in the brain. After that first pharmacological action, which is relatively -- we can measure that. What happens in the next half a minute to many weeks is complicated.

Q. Okay. And Biederman, in the study he did in 1989 that we already talked about, he said he didn't see a distinction between the placebo and the desipramine-treated group until the third week; is that right?

A. That is what he said. And that contradicted data from other studies.

Q. But that was Dr. Biederman; right?

A. That was Dr. Biederman's study. I think there were other studies where you didn't see that.

Q. Do you know whether the activity of tomoxetine in treating ADHD is immediate or delayed?

A. No, I don't know. And I think part of the -- it's complicated when you read the literature because people say different things. Sometimes they're referring to the maximal response, which can take a little bit of time. Sometimes they say it's immediate. It isn't as clear a story, but when you compare the psychostimulants, which are norepinephrine and dopamine reuptake blockers, with the tricyclics, which have an action of blocking norepinephrine

and serotonin, it's a reasonable -- I think a person of ordinary skill in the art would assume it's the reuptake blockade that leads to a relatively rapid effect.

Q. The uptake blockade occurs immediately; right?

A. The uptake blockade occurs immediately, and like we showed in Donnelly, like Donnelly reports, it's a fast response.

Q. And Biederman reports that it wasn't a fast response.

A. A delay, and he speculates, well, maybe there's some ramping up, and although the end result is the same, the pharmacology is complicated, and if you start giving low doses, there are these compensatory receptor actions that occur, and, you know, it just gets complicated at that point.

Q. It is indeed very complicated; that, we can agree. Right?

I need an audible answer.

A. Well, it is complicated how all this plays out. The pharmacology is straightforward. That's why we focus on pharmacology in drug development. We don't start to worry about the circuitry or the biology of the disorder.

Q. You don't; right?

A. No. Drug discovery doesn't.

Q. And --

A. Prozac, the development of Prozac didn't.

Q. Since that was our drug, I suspect we may know a little more about that than you. Do you agree?
A. It depends --
THE COURT: Well, I don't want to know anything about it.
(Laughter)
THE COURT: Stick to this drug.
MR. LIPSEY: I've always wanted to reargue that case, Your Honor, because Mr. Hurst right here took it away from me at the 11th hour.
THE COURT: Take it to Philadelphia.
(Laughter)
Q. The effects of the tricyclic antidepressants, including desipramine, on the brain of humans in connection with their action on ADHD were quite complex; correct?
A. I think the pharmacological actions are not that complex. The biology, how that pharmacological action translates into changed behavior is complicated. The pharmacology is not that complicated. It's more complicated than atomoxetine, but it isn't that complicated. We know a lot about the pharmacology of these drugs.
MR. LIPSEY: Your Honor, it is 3:55.
THE COURT: Yes, it is.
MR. LIPSEY: I would dearly love an opportunity to renew my notes. I'm reluctant to keep everybody here. I

suspect if I do, I will either have either nothing or something very brief for the witness in the morning.

THE COURT: I assume there's going to be some redirect.

MR. ROCKEY: Not sure, Your Honor. Right now, I don't think so. If there were --

THE COURT: Is this gentleman going to be here tomorrow?

MR. ROCKEY: Yes.

THE COURT: All right. Well, then, I'm not so worried. I was fearful that we were keeping him from beautiful Wisconsin. I didn't want to do that.

You know what I think we'll do? I think we'll break for today. The doctor has been on the stand in a long hot afternoon, and I think he should probably take a break, too.

THE WITNESS: Thank you, Your Honor.

THE COURT: So why don't we take a break for today. We will resume tomorrow.

Who is your next witness?

MR. CLEMENT: Mr. Goolkasian, Your Honor.

THE COURT: So we will have our next witness ready to go?

MR. CLEMENT: Yes, Your Honor.

THE COURT: And any witness after that?

MR. PARKER: Yes, Your Honor. Dr. James Johnson.

THE COURT: And that witness will also be present or available?

MR. PARKER: Yes, he will, Your Honor, and I suspect that we probably won't finish direct on Wednesday, probably have to carry over into the following week. But he's available.

THE COURT: Okay. We're only going to go tomorrow until about 3:30.

We'll see you all tomorrow at 9 a.m. Have a good night.

(Matter adjourned until Wednesday, May 19, 2010, commencing at 9 a.m.

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